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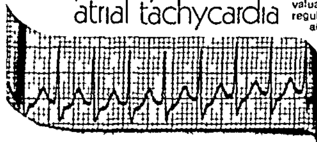
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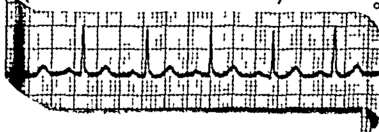
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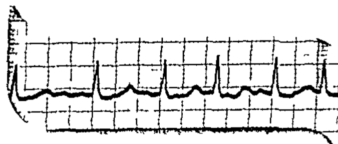
In paroxysmal atrial tachycardia the drug *slows the ventricular rate* and also is valuable in restoring the heart to a regular sinus rhythm.[3] Paroxysmal *atrial tachycardia induced by ex*ercise has uniformly been prevented by propranolol and *results with INDERAL in the* Wolff Parkinson White syndrome have been favorable *in all but a few patients reported*. This condition appears to be one of the more definite indi*cations for propranolol*.

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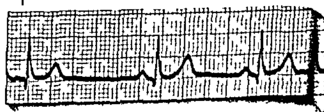
Sinus tachycardia induced by stress *may be inappropriate to the needs* of the patient and in fact may be causing symptoms of itself. If the *clinical situation does not sug*gest a needed compensatory sinus tachycardia and the heart *rate is indeed inappropriate* treatment with propranolol has been successful.

tachycardias and arrhythmias due to thyrotoxicosis



Although propranolol may accomplish only the reduction of the heart rate in hyperthyroidism it has *proved useful for this purpose. Sinus tachycardia* in hyperthyroidism which causes symptoms may be relieved by the administration of *propranolol before definitive therapy*. The author has observed that atrial fibrillation complicating hyperthyroidism was easily terminated *using modest doses of propranolol*.

persistent atrial extrasystoles



In cases of atrial premature beats frequent enough that they could herald the onset *of atrial fibrillation* it has been recommended that propranolol be used after other measures ha failed to control the b

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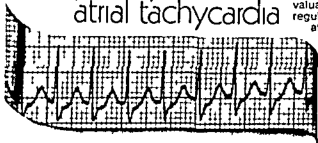
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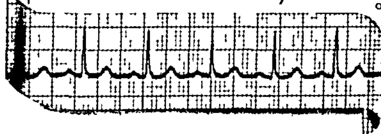
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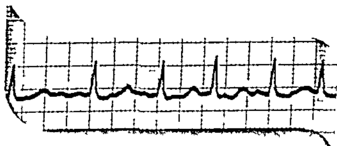
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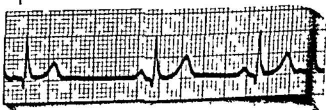
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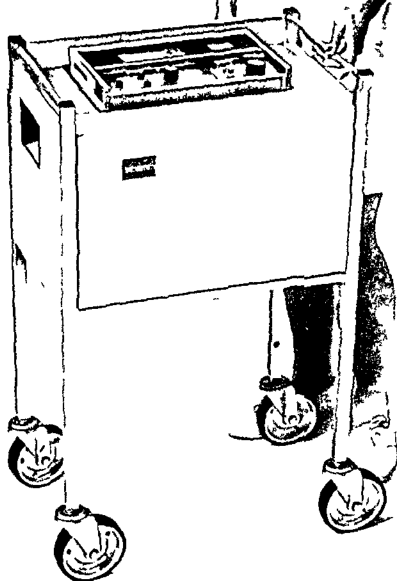
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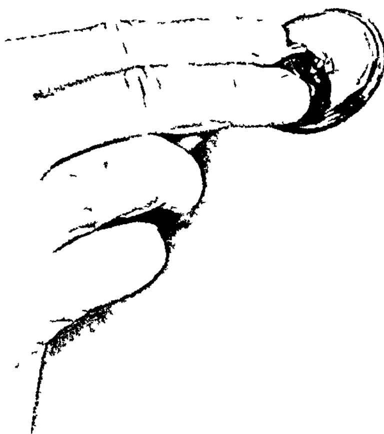
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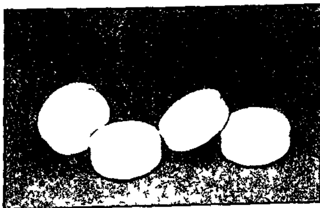
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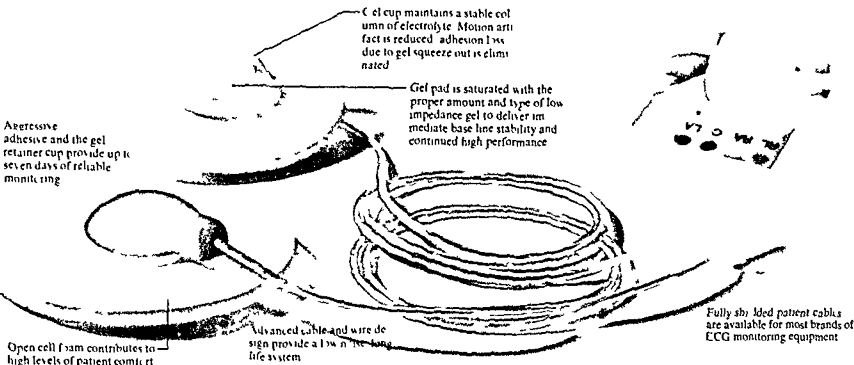
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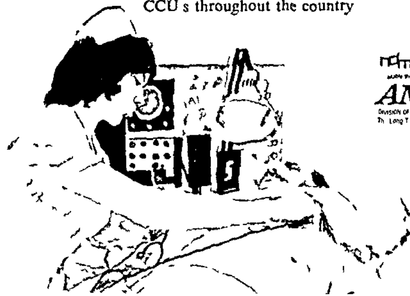
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Editorial

Paleocardiology and neocardiology

Malcolm Carruthers M D M R C Path M R C G P
Peter Taggart M R C P (Lond.) M R C P (Edin)
London England

The speed with which coronary heart disease has become the Western way of death appears in several important respects to have outpaced the rate of change in cardiological practice This largely twentieth century disease might be considered to be a biochemical disorder resulting from a wide variety of agents present in the Western way of life Therefore if the fight against this modern epidemic can be termed neocardiology its major emphasis should logically be on metabolic management guided by general medical and epidemiological principles More of the current training and practice seems however to be based on the older paleocardiology" applicable to the congenital and valvular heart disease which forms a decreasing fraction of the total clinical problem

This article tries to partially redress this balance by consideration of some points in the field of detection and prevention of coronary heart disease

Detection

It is difficult to escape the conclusion that the currently accepted way of detecting coronary heart disease is to wait until the subject presents with angina or heart attack There are several objections to this approach After a heart attack the mortality rate is increased by a factor of five according to the figures quoted in the report of the Inter Society Commission for Heart Disease Resources[1] The same authoritative text points out that approximately 25 per cent of patients die within three hours of the onset of infarction and a further 10 per cent die during the next few weeks Any method of detection which kills a third of the people in whom it establishes the diagnosis of what in many persons is likely to be a preventable condition is surely unacceptable

Some degree of atherosclerosis is present in the majority of the Western population Deciding in a particular individual whether it will cause symptoms even over a limited period, such as five years means dealing in probabilities rather than certainties The weighting of the e risk factors can be done in the head, on a risk calculator or on a computer[2] according to inclination and facilities With the availability of a large amount of hard statistical data on a wide range of factors influencing prognosis the last of these methods, operated with a manual override of clinical judgment, would seem an immensely valuable tool for the neocardiologist

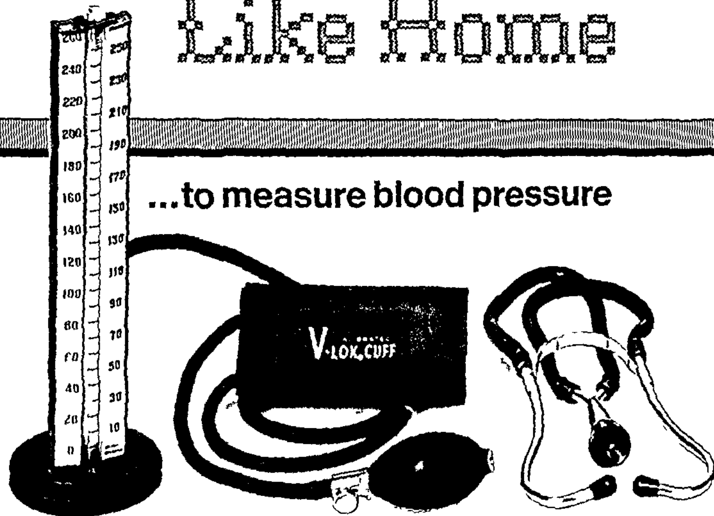
To a certain extent, this type of approach has been accepted for life insurance and statutory examinations as for a pilot s license Apart from examples of people suffering heart attacks immediately after being declared fit by the life in

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Repri t requests to Dr M lcolm Carruthers Departme t of Research Chem cal Pathology St. Mary s Hosp tal Med c l School London W2 1PG Engla d.

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(1)Reference *Medical World News Cardiovascular Review* '73 Burch G E *Chairm* epartment Medi Tulane University School of Medicine *New Orleans*

overload resulting from impaired left ventricular function [11] The simplicity and noninvasive nature of these techniques make them additionally attractive

The resting electrocardiogram (ECG) is well known to be an unsatisfactory method of screening for coronary heart disease Even during the acute phase of myocardial infarction the recording may be equivocal in as many as 50 per cent and normal in a further 25 per cent.[12] These dangers of over reliance on the resting ECG were voiced by one of its innovators Mackenzie [4] who said of it Some light can be thrown upon abnormal actions of the human heart but beyond this the great majority of the variations are beyond interpretation and have become a field for much vain speculation Further anxiety and the consequent increase in sympathetic activity can result in ST T segment changes which may mimic those commonly associated with ischemia [13]

Exercise testing on the other hand, could well have a useful part to play in spite of the frequently expressed reservations in relation to statutory examinations [14] Mason and his colleagues[15] compared coronary arteriograms of two groups of 42 patients, one having positive ST responses to near maximal exercise and the other normal responses. Using 50 per cent occlusion as their criterion they noted 9 5 per cent of false positive and 26 per cent of false negatives A higher false negative rate was reported by Roitman and associates [16] although further refinements of this technique have probably lowered the incidence of false positive results still further and increased its prognostic value [17] The incidence of false negatives has also recently been reduced by about 10 per cent using altered lead systems [18] More recent evidence suggests that computer analysis may improve this by 10 to 20 per cent.[19] While accepting that exercise testing remains far from perfect as a diagnostic tool its usefulness as an adjunct to other methods is clear and it is likely to become more valuable with further development

An added factor in favor of combining the resting and exercise ECG with apex cardiography and phonocardiography particularly in statutory examinations is that they are together less prone to interference by undeclared medication such as β blocking drugs This powerful new range of compounds can convert the ECG of anxious individuals and some subjects with ischemic heart disease to normal [13] It can also reduce elevated blood pressure plasma lipid, and glucose levels [20] In certain situations gas chromatographic analysis of blood or urine samples may be needed to exclude these drugs

Biochemical tests It is probably in this area that the greatest advances in the detection of latent cardiovascular disease are being made Few of these tests which are becoming increasingly accepted on an epidemiological basis, are yet applied in routine cardiological practice for several reasons

First paleocardiological consideration of lipids was usually limited to isolated cholesterol determination in random serum samples Even this was of sufficient predictive value to be included as a major risk factor in most studies The tendency to equate ' lipids with cholesterol estimation is partly due to the ease and antiquity of the methods but more particularly because fasting blood samples are not needed. Recently however triglyceride estimation has come to be regarded as important in the detection of clinically significant hyperlipidemias [21] This estimation is preferably carried out on samples taken after an overnight fast although some measure of endogenous triglyceride can be obtained by the more laborious methods of ultrafiltration or ultracentrifugation[22] of nonfasting samples Again in fasting samples free fatty acid levels are a good index of the intensity of sympathetic drive component in atheroma formation [23] In this context they have been found to be higher in the coronary prone individuals showing the Type A behavior pattern [7] Further they have key roles in both lipid and carbohydrate metabolism. These factors together with their increased ease and precision of analysis by the recently developed semi automated fluorimetric method [24] should warrant their inclusion with cholesterol and triglycerides in the trio of lipid measurements making up a routine neocardiological examination

There is greater uncertainty over the place of measurements of carbohydrate metabolism in the diagnosis of diseases of the cardiovascular system Apart from the increased incidence of atheromatous arterial disease in diabetes and the impaired carbohydrate tolerance of some patients with atheroma formal glucose tolerance testing with measurements of plasma insulin has

surance examiners, the limitations of the techniques conventionally applied were tragically demonstrated by the British Trident disaster in June, 1972 According to the Civil Aircraft Accident report published this year [3] the underlying cause of this disaster was incapacitation of the captain flying the aircraft by an abnormal heart condition ' The degree of abnormality of the coronary arteries which can go undetected in a standard examination carried out only seven months previously is shown by the postmortem findings in this case Apart from evidence of a small resolving thrombus and antemortem intimal tear both in the left coronary artery, all three coronary arteries showed throughout their length severe atherosclerosis" such that in places, at least the effective diameter of the lumen had been reduced by 50 per cent to 70 per cent '

The difficulties in distinguishing those with little or no atherosclerosis from those with an advanced form of the disease become apparent when the range of routinely applicable diagnostic criteria is considered

The history The history of the high risk coronary candidate is characteristically brief As Osler[4] observed in 1910 when coronary heart disease was still rarely described It is not the nervous individual who suffers heart disease but the robust ambitious man the indicator of whose engines is always set at full ahead This never sick rather than never well' approach is usually reinforced by a high denial rate on direct questioning for symptoms which is naturally greater during statutory examinations Even so increasing day long fatigue and limitation of physical exertion by breathlessness or a feeling of exhaustion are likely to be some of the earliest symptoms and were repeatedly emphasized by Mackenzie[5] half a century ago

Taking the history and direct questioning on the ability to cope with problems at home and at work may conflict with the picture given by wife or employer, but should give some indication of the social stress to which the individual is subject If calculated formally life stress has been shown to be related not only to biochemical variables such as catecholamine excretion but also to the short term incidence of several diseases, including coronary heart disease [6]

The individual s response to psychosocial stress is also of considerable prognostic importance according to the mass of evidence provided by the Western Collaborative Group Study [7] This classification into active, aggressive competitive time and deadline conscious Type A behavior the reverse Type B behavior, and subtyping according to intensity, is at the stage where it can be incorporated with the social stress rating into the computerized diagnostic matrix [8]

General physical examination The appearance of the coronary prone individual was also described by Osler[4] as typically having a military bearing with steel gray hair The addition of a mustache frequently intensifies the determination written into every part of the face and may bear some relation to the behavior pattern Apart from this, the premature aging of the arteries is often reflected in the presence of frontal baldness and corneal arcus In a recent study carried out in Cambridge, the incidence of both these features was highly correlated with the presence of cardiovascular disease [9] The presence of skin or tendon xanthomas is strongly suggestive of moderate or severe hypercholesterolemia

The body build is also of importance short, stocky endomorphs being considerably more coronary prone than tall thin ectomorphs The habitus may have an influence for psychological as well as physical reasons Obesity alone has been shown to have less of an effect than was at one time implied by life insurance figures [10] In a large scale five year prospective study it was found that having corrected for age blood pressure, cholesterol and smoking habits no further accuracy of prediction could be obtained by including indices of body mass index skinfold thickness, or relative body weight in the calculations Given that obesity operates mainly by its action in causing hypertension and hyperlipidemia with elevations in cholesterol, triglyceride and free fatty acids it would appear better to include these separately measurable end effects rather than just one of the proximal causes

Cardiological examination Physical signs in the cardiovascular system are generally inconspicuous in persons with early coronary heart disease The apex cardiogram and phonocardiogram have been shown to be useful in some instances in detecting the presence of an atrial gallop consequent upon a raised left ventricular end diastolic pressure and volume

careful regulation guidance and instruction preferably at purpose built centers as exist in certain parts of Europe but which are conspicuous by their absence in America and Britain

Given these safeguards a varied exercise program can be built up to meet individual needs and preferences Suitably vigorous activities include swimming cycling rowing or even jogging[27] For most urban dwellers gymnastics is most easily organized regulated and packaged in a condensed form A study sponsored by the Medical Research and Sports Councils at the City Gymnasium in London[28] has indicated that greatly improved cardiorespiratory fitness and reduction in lipid levels can be obtained in middle aged business executives and patients undergoing cardiac rehabilitation by as little as fifteen minutes of intensive exercise two or three times each week Further evidence of the modest amount of exercise time needed to provide considerable protection from heart disease is given by a recent study of the leisure time activities of British Civil Servants[29] Half an hour s vigorous activity defined as over 50 per cent of maximum oxygen consumption reduced the incidence of heart attacks to a third of that in the inactive control population Similar benefits in secondary prevention have been shown in America[30] and reduction of lipid levels with a few notable exceptions in the case of cholesterol[31] usually found with vigorous exercise providing diet is kept constant and seasonal variations ruled out The importance of balancing physical and mental activity is not exactly a new idea In the dialogues of Plato[32] Timaeus states Avoid exercising either mind or body without the other and thus preserve an equal and healthy balance between them So anyone engaged on mathematics or any other strenuous intellectual pursuit should also exercise his body and take part in physical training By such moderate motion he can reduce to order and system the qualities and constituents that wander through the body After more than 2 000 years it appears difficult to improve on this advice

A similar approach to primary prevention is being adopted in Multifactor Preventive Trials in Ischemic Heart Disease supported by the Regional Office for Europe of the World Health Organization After a less detailed assessment than the one outlined here separate and combined modification of smoking blood pressure cholesterol weight exercise and psychological factors are being attempted in a wide variety of constituent studies Also in secondary prevention considerable improvement in post-myocardial infarction mortality has been observed following physician assisted implementation of risk factor control[33]

The arguments in favor of this neocardiological approach to both the primary and secondary prevention of ischemic heart disease appear formidable and were cogently argued by Raab[34] one of its originators The report of the Inter Society Commission for Heart Disease Resources[1] set this theme for the seventies by firmly stating that major progress in controlling atherosclerotic diseases is possible only by primary prevention This must be the main strategic thrust of a national effort to control coronary heart disease during the years ahead. It also emphasized the economic stakes in that for 1967 the direct cost to America from arteriosclerotic and related diseases was 4 3 billion dollars with indirect costs due to deaths estimated to be several times greater Individual companies can calculate their loss in terms of the cost of their being deprived of some of their most dynamic employees Organizations such as airlines can weigh up the cost of losing a constant proportion of their most valuable manpower together with the multimillion dollar equipment they handle

Such neocardiological monitoring of cardiovascular health of high risk groups by techniques which can mainly be applied by paramedical personnel and assessed by computer combined with a positive approach to risk factor modification would be socially and economically justified if it produced just a modest reduction in heart attack rates

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yet to prove its worth in this situation If a fasting sample is being taken for lipid estimation, a single glucose determination would help in excluding preclinical diabetes with its impaired prognosis There appears also to be some obscure relationship between high blood uric acid levels and cardiovascular disease, though this measurement is seldom taken into account as a risk factor

One significant feature of lipid estimations is their variability in one individual from month to month and year to year This was dramatically demonstrated in a group of American Air Force personnel having samples taken at approximately three monthly intervals over five years[25] Fluctuations of up to 25 per cent of the mean cholesterol level occurred frequently, but in the 16 individuals who suffered heart attacks there were rapid repeated swings of over 50 per cent in the preceeding months with even greater variability in total lipid levels This pattern of phasic lipid changes related to periods of emotional stress with a high anger and frustration content was considered of serious prognostic significance Similar oscillations in cholesterol levels were associated with the phasic stress in the life of tax accountants[6] Smaller seasonal variations occur in cholesterol triglycerides and free fatty acids These could be allowed for in any computerized assessment of the lipid profile in relation to prognosis and judging the efficacy of treatment

Prevention

A wide range of tried and tested methods of reducing the incidence of coronary heart disease is available without the need for any new scientific miracles If the population could be induced to eat and smoke less, reduce their stress levels and take more of the right sort of exercise one could confidently expect to decrease the number of heart attacks to a fraction of their present level[1] The large residual problems are ones of identification and motivation

Identification of the high risk individual should be possible with considerably improved accuracy and at reasonable cost if the suggested methods of examination were used at yearly intervals or more frequently where indicated Calculation of the desirable interval before the next examination could be one of the functions of computerized assessment A further development of this would be if the computer programmed with past and present results could indicate possible lines of treatment in order of magnitude of probable benefit for that individual Application of the most suitable preventive measures to those at greatest risk offers the most economic use of therapeutic resources

Motivation is probably the greatest stumbling block in any program of prevention involving major changes in life style such as stopping smoking, taking up exercise, or keeping to a diet. There is likely to be a great deal that could be learned from market research organizations on improving the acceptability of such measures First, there is market identification, i e, those whom tests show to be most at risk Then there is the presentation of an acceptable range of "goods to allow scope for individual choice of action together with the 'after sales service' and feed back of information on effectiveness to the consumer The range is certainly broad enough to suit most tastes and each has its ardent advocates with a body of evidence to prove their case Lipid and blood pressure-lowering drugs abound probably because they require the least effort on part of patient and physician alike Except as an essential part of the treatment of the relatively rare true inborn errors of fat metabolism the benefits of dietary measures appear to be geographically distributed. Greatest benefit is described in Scandinavia, less in America and least in England These differences may be due to whether the trials involve a captive population in institutions or 'free range' individuals and the excess of fat normally eaten

Exercise is emerging as one of the most potent weapons in the armory of the neocardiologist It is one of the few positive methods available for improving cardiovascular health, and as such is likely to appeal to the positive driving individual most prone to coronary disease

It could be considered as one way in which he can indulge his addiction to norepinephrine while at the same time offsetting its harmful effects. It may also have the invaluable side effects of anxiety reduction or even cessation of smoking Like most strong drugs, its dosage needs to be increased gradually, particularly in unfit and overweight individuals Avoidance of sudden maximal efforts and extremes of temperature are very important especially in the early stages The whole reconditioning process needs

Clinical communications

Interpretation of RSR' in pulmonic stenosis

R. Curtis Ellison, M.D.*
Washington, D.C.
Olli S. Miettinen, M.D., Ph.D.
Boston, Mass.

For The Joint Study on the Natural History of Congenital Heart Defects*

It has been suggested that in pulmonic stenosis (PS) a ventricular complex with an RSR' pattern in Lead V_1 tends to indicate less severe disease than does a "pure R" wave.[1-5] The present study was undertaken (1) to test this proposition in a large series and (2) to determine how the magnitude of the R' voltage relates to that of "pure R" at comparable levels of PS severity.

Patients and methods

The data were derived from a national collaborative follow-up study of three congenital heart defects. A total of 603 nonoperated patients with isolated valvular PS demonstrated at cardiac catheterization were admitted to that study. The admission data of 539 of these patients were analyzed. The primary reason for exclusion was incompleteness of data. Also, in order to prevent difficulty in interpretation due to bundle branch block, any patient was excluded if the QRS duration exceeded the following limits: for infants in their first year of life, 80 msec; in the 1 to 7 year category, 90 msec; and in patients 8 years of age or older, 100 msec.

Measurements of right ventricular systolic pressure (RVSP) and gradient across the pulmonic valve (PVG) were made at routine cardiac catheterization with the patient in a resting state and under light sedation (a mixture of demerol 25 mg. per milliliter, phenergan 6.25 mg. per milliliter, and chlorpromazine 6.25 mg. per milliliter in a dosage of 1 ml. per 20 pounds of body weight up to a maximum dose of 2.0 ml.).

Measurements of the R, S, and R' voltages of Lead V_1 had been made from the standard electrocardiogram at the participating clinics. The ventricular complex was classified as an RSR' pattern if in the positive deflection there was a notch which returned to or reached below the isoelectric line and if the second positive component exceeded the first (R' > R). There were 108 patients with such an RSR' pattern (R' Group), leaving 431 patients with an R pattern (R Group). (The latter group included 17 patients who had a second positive deflection which was smaller than the first. These second deflections averaged only 2.6 mm. and a multivariate analysis indicated that they were uninformative in estimating RVSP or PVG.)

The R' and R groups had similar distributions of age and QRS duration. The median ages were

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Reprint requests to: O.S. Miettinen, M.D., Department of Epidemiology, Harvard School of Public Health, 665 Huntington Avenue, Boston, Mass. 02115.

*Present Address: Pediatric Cardiology, Georgetown University Hospital, 3800 Reservoir Rd., N.W., Washington, D.C. 20007.

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Equivalent R = (0 5) R + 2 mm

Thus when utilizing the voltages in Lead V_1 in attempting to estimate severity in pulmonic stenosis an observed R voltage is estimated to have the same meaning as an R voltage whose magnitude is one half the R deflection plus 2 mm For example an R magnitude of 20 mm would be the equivalent of a pure R magnitude of

(0 5) 20 mm + 2 mm = 12 mm

When using PVG in place of RVSP the equivalence relationship between R and R was identical to that determined with RVSP

Table 1 Comparison of RVSP and PVG in R Group and R Group

	R Group (n = 108)	R Group (n = 431)
RVSP		
Range	31 205 (mm Hg)	28 260 (mm Hg)
Mean	73	89
Median	71	79
PVG		
Range	14 190	15 240
Mean	55	70
Median	51	59

RVSP = right ventricular systol c p essure
PVG = pulmon val e gradient

Discussion

One goal of the Natural History Study of congenital heart defects has been to attempt to estimate severity from the clinical picture electrocardiogram and chest x ray At the onset of this endeavor in PS it was found that 20 per cent of the patients showed an RSR pattern in Lead V_1 with a dominant R wave Since the voltage of the dominant positive deflection in Lead V_1 is one of the factors utilized in the assessment of severity (the final result of which will be presented in a subsequent publication) this study was designed primarily to determine how the magnitude of an R wave should be interpreted in comparison with an R wave in the estimation of severity in PS

Although an RSR pattern in Lead V_1 is more frequently associated with the presence of an atrial septal defect or other type of volume overload of the right ventricle it is not uncommonly found in patients with PS Most investigators report that such cases usually show only mild or moderate degrees of obstruction the pattern is rarely seen in patients with severe disease [1 5]

The mechanism producing this pattern in patients with PS is unknown Studies by Blount Munyan and Hoffman[3] of atrial septal defect indicated that the terminal forces producing an R in Lead V_1 resulted from hypertrophy of the outflow tract of the right ventricle Boineau Spach and Ayers[6] produced a similar electrocardiographic pattern by creating atrial septal defects in dogs They found the pattern to be related to dilatation of the right ventricle and hypertrophy of the high free wall of the right ventricle and of the crista supraventricularis no evidence for abnormalities in the conducting system were found. Fowler[4] found a pattern of terminal conduction delay by vectorcardiogram in a high percentage of patients with mild PS he suggested mild dilatation of the right ventricle similar to that occurring in atrial septal defect as a possible mechanism for the vectorcardiographic finding

The present study supports the contention that in PS the presence of an RSR pattern in Lead V_1 suggests less severe disease than the presence of a QR R or RS pattern However the severity difference between patients with a dominant R and those with an R wave appears to be rather small and the severity varies widely in both groups The study also suggests that for a given voltage of a dominant R wave the severity tends to be lesser than for a pure R wave of equal magnitude Thus for any given R there is a smaller equivalent R corresponding to the same degree of severity Use of the attenuated value for R should improve the correlation between the electrocardiogram and the hemodynamic state in patients with pulmonic stenosis

Summary

An RSR pattern in Lead V_1 (with R the dominant positive deflection) was found in 108 of 539 patients (20 per cent) with valvular pulmonic stenosis admitted to a national co operative study of congenital heart defects On the average patients with an RSR pattern showed lower right ventricular to pulmonary artery pressure gradients (mean = 55 mm Hg) than patients with a QR R or RS pattern (mean = 70 mm Hg) Moreover an R wave of a given voltage was associated with generally lower right ventricular systolic pressures and gradients than an R wave of equal amplitude Quantitatively these data

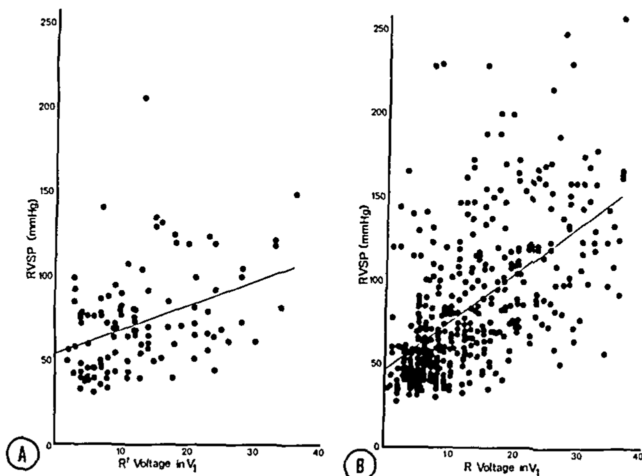


Fig 1 *A* The right ventricular systolic pressure (RVSP) related to the voltage of the R wave in Lead V_1 in 108 patients with pulmonic stenosis and an RSR pattern The regression equation is RVSP (mm Hg) = 54 2 + (1 45) R where R is deflection in millimeters (1 mm = 0 1 mV) *B* The right ventricular systolic pressure related to the voltage of the R wave in Lead V_1 in 414 patients with pulmonic stenosis and a pure R wave in Lead V_1 between 1 and 36 mm The regression equation is RVSP (mm Hg) = 47 4 + (2 92) R where R is deflection in millimeters (1 mm = 0 1 mV)

9 4 and 8 4 years respectively with ranges from 0 0 to 52 years and from 0 1 to 50 years respectively For QRS duration the mean values were 76 msec for the R Group and 73 msec for the R Group

The severity implications of the presence of an RSR pattern were evaluated by comparing the R and R groups with respect to the distributions of RVSP and PVG

To evaluate what *magnitude* of R compares to a particular value of R in terms of similar severity RVSP and PVG were related to the voltage of R in the R Group and to that of R in the R Group The respective regression parameters were compared

Results

The values of RVSP and PVG in the R Group were generally lower than in the R Group as shown in Table I

The relationship of RVSP to voltage is shown separately for the R and R groups in Fig 1 For the R Group the regression equation is RVSP (mm Hg) = 54 2 + (1 45) R and for the entire R Group it is RVSP (mm Hg) = 50 3 + (2 66) R where the voltages are entered in terms of millimeters deflection (1 mm = 0 1 mV) In Fig 1 *A* all 108 patients with an RSR pattern are shown Fig 1, *B* shows the 414 patients of the R Group who had values of R between 1 and 36 mm which corresponded to the range of voltages found in the R Group for these 414 patients RVSP (mm Hg) = 47 4 + (2 92) R

The above equations indicate a significantly greater increase in RVSP for a given increase in voltage for a pure R wave than for an R wave (for the slope difference two sided p=0 001) From the regression equations it is possible to determine an equivalent R magnitude for a given R voltage

Postoperative recurrence of angina pectoris after aortocoronary venous graft bypass

Alberto Benchimol M D
Harold Fleming M D
Kenneth B Desser M D
Charles L Harris M D
Phoenix, Ariz.

Aortocoronary saphenous vein bypass graft implantation is currently the most frequently employed surgical procedure for the treatment of coronary artery disease[1] Most published studies of patients so treated have presented data regarding postoperative graft patency effects of the procedure on myocardial function and success rates for the relief of preoperative angina pectoris[1-6] No previous workers have examined, in detail the postoperative recurrence of angina pectoris in subjects with such grafts We report here findings in twelve patients who experienced a recurrence of angina pectoris after a postoperative interval free of symptoms

Material and method

Fifty six patients with stable preoperative angina pectoris comprised the study group All subjects underwent complete left and right heart catheterization and selective coronary arteriography before and after aortocoronary saphenous vein bypass implantation Postoperative catheterization was performed an average of six months after operation in the study group Aortocoronary bypass grafts were considered occluded if there was absence of saphenous vein segment opacification during introduction of radio opaque dye into the graft origin and lack of retrograde opacification of the graft during native coronary arteriography Significant progression of coronary artery disease was considered present when the degree of arterial obstruction in any single vessel had progressed to over 50 per cent of the luminal diameter in the interval between the two studies All subjects were interviewed by the physician staff prior to and after operative intervention The diagnosis of angina pectoris was made in the postoperative period only if the nature and quality of chest pain was identical to that experienced in the preoperative period. The degree of physical activity and adjunct medical therapy such as low fat diet coronary vasodilators anticoagulants tranquilizers and beta blocking agents were recorded for each patient

Results

All 56 subjects had complete relief of angina pectoris after the aortocoronary bypass procedure This included absence of anginal pain at rest during physical activity emotional upset and in the postprandial state Twelve patients had a subsequent recurrence of chest pain identical with that which was present prior to the operation The average onset of pain was two months into the postoperative period. Based on clinical and cardiac catheterization data an attempt was made to determine whether or not there were any apparent differences between findings in the twelve subjects in whom angina pectoris recurred (Group I) and the asymptomatic group (Group II)

There was no significant difference between the degree of physical activity or adjunct medical therapy in the two groups Of a total of 20 bypass grafts implanted in Group I 14 (70 per cent) were patent this figure was similar to the patency rate

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Reprint requests to Dr Alberto Benchimol Good Samaritan Hospital, P O Box 2989 Phoenix, Ariz. 85062

suggest that in patients with an RSR complex in Lead V_1, the R voltage has the same severity implication as a 'pure R' of magnitude (0 5) R + 2 mm

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Effect of nitroglycerin and papaverine on coronary flow in man

Hendrick B Barner M D
George C Kaiser M D
Vallee L Willman M D
St Louis, Mo

Nitroglycerin is widely utilized in the management of angina pectoris but there is disagreement concerning its effect on coronary flow in man Coronary flow measurement by nitrous oxide [1] ^{84}rubidium coincidence counting [2-5] radioactive ^{85}krypton [6] and radioactive ^{133}xenon [7,8] has revealed an increase decrease or no change in coronary flow after nitroglycerin in patients with and without coronary artery disease However these techniques do not detect transient changes in blood flow More recent use of methods that discriminate evanescent flow changes again do not give consistent results A nonquantitative method [9] indicates an increase in coronary flow after nitroglycerin while two quantitative studies indicate that there is no significant change [10] or a decrease in coronary flow [11]

In this study the electromagnetic flowmeter has been used to measure flow in coronary bypass grafts in response to intra arterial and intravenous nitroglycerin which is compared with papaverine

Method

Mean blood flow was measured in 28 saphenous vein coronary bypass grafts in 22 patients operated on for chronic angina pectoris Studies were performed during hemodynamic stability 20 to 30 minutes after discontinuation of cardiopulmonary bypass Transfusion with whole blood was continuous to replace concurrent loss

Flow probes (Carolina Medical Electronics 400 Series) were laboratory calibrated in a gravity flow system using a canine arterial segment and canine blood with a hematocrit of 35 per cent and a temperature of 33 to 35 C Timed collections of blood were made in the flow ranges found clinically and the probes were accurate to ± 8 per cent Arterial pressure was measured with a 16 gauge radial artery cannula and a Statham P23Db strain gauge Data were continuously recorded on a direct writing recorder (Brush Mark 260)

Nitroglycerin tablets were sterilized with ethylene oxide diluted with physiologic saline to a concentration of 0 2 mg per milliliter less than 10 minutes prior to use and passed through a Millipore filter (Millipore Corporation Swinnex 13 SXHA 013 os 0 45μ) Nitroglycerin (0 4 mg) was given intravenously as a 2 ml bolus and papaverine (30 mg) was given as a 1 ml bolus intra arterial nitroglycerin (0 1 mg) and papaverine (15 mg) were given into the bypass graft as a 0 5 ml bolus over five seconds Two patients received sublingual nitroglycerin (0 4 mg) and three patients received physiologic saline 0 5 ml intra arterially

Mean arterial pressure was calculated by adding one third of the difference between the systolic and diastolic pressure to the diastolic pressure Peripheral resistance (millimeters of mercury per milliliter per minute) was calculated as the quotient of mean arterial pressure (millimeters of mercury) and mean flow (milliliters per minute) Data were calculated every 15 seconds for one minute every 30 seconds for two minutes and then at one minute intervals until return to control level or stabilization

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Rep int requests to Hendri k B Barner M D Department f S g ry St Louis Un rsity 1325 S G nd St Louis M 63104

in Group II (55/78 71 per cent) Six of the twelve patients in Group I had at least a single occluded graft Of 44 patients in Group II 21 patients had at least one graft occlusion Only a single subject in Group I had occlusion of all grafts implanted whereas eight patients in Group II, who repeatedly denied angina pectoris had documented occlusion of all grafts When postoperative coronary arteriograms were compared with those obtained prior to operation it was found that the total progression of atherosclerotic disease was comparable in the coronary arteries of both groups There were no discernible differences between the degree of obstructive coronary arterial disease or clinical status of subjects in the two groups prior to operative intervention

Discussion

A complete remission of angina pectoris subsequent to bypass graft implantation and recurrence of symptoms in 20 per cent of the patients so treated are in accord with statistics cited in the existing literature on the subject [1-4] However as demonstrated in this study the factors which result in the reappearance of angina pectoris after the aortocoronary bypass graft procedure are elusive It is indeed remarkable that there were no discernible differences in the clinical and laboratory parameters examined in the two groups Denial of angina pectoris in eight patients who had occlusion of all grafts yet had unequivocal angina pectoris prior to the operation is remarkable and disconcerting It is possible that such major traumatic intervention and preconceived notions concerning the operative procedure itself played a significant role in the relief of pain The psychologic implications of operative procedures developed for the treatment of angina pectoris have been well established [7] It is clear that in our series of patients neither patency of graft nor progression of coronary arterial disease was related to the reappearance of angina pectoris The mechanisms which govern the development of angina pectoris are in general complex and still incompletely understood

These data are not presented in order to cast discredit on the aortocoronary bypass procedure but demonstrate that presumed correlations between graft patency and relief of symptoms although logical are not a universal experience Since aortocoronary bypass has not been demonstrated to prolong the life of subjects so operated upon the major current indication for surgical intervention is the possible relief of angina pectoris

Based on the experience described in this paper it is proposed that caution be exercised before assuming that there is a significant relationship between aortocoronary bypass graft patency and the relief of angina pectoris

Summary

Fifty six patients with angina pectoris underwent aortocoronary bypass graft implantation All subjects had an initial angina free postoperative period Twelve patients so operated upon had a return of angina pectoris their clinical and catheterization findings did not differ in any respect when compared with those in the pain free group Eight subjects with occlusion of all aortocoronary grafts denied postoperative angina pectoris It is concluded that caution should be exercised in attributing the relief of angina pectoris to aortocoronary bypass graft patency

We wish to acknowledge the technical assistance of Nancy Copeland R N Carole Crevier Larry Kuriger Sidney Peebles Jeanette Goff and Les Zendle

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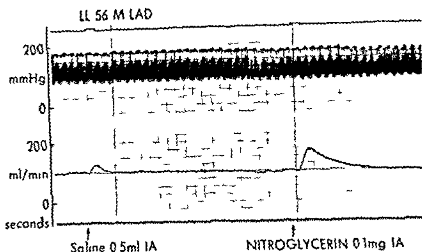


Fig 3 Mean arterial pressure (upper trace) and coronary graft flow are shown in response to intra arterial injection of physiologic saline and nitroglycerin.

Discussion

These studies demonstrate an increase (maximal 4 per cent) in coronary bypass graft flow lasting 15 to 30 seconds followed by a decrease (maximal 23 per cent) in flow lasting five minutes as mean arterial pressure fell 24 per cent after intravenous nitroglycerin (0 4 mg) These observations are similar to those in a comparable study[10] in which a smaller dose of nitroglycerin (0 15 mg) was used and resulted in an increase in coronary flow in only one out of five patients and a smaller nonsignificant (10 per cent) decrease as mean arterial pressure fell 27 per cent These differences may be attributed to the smaller dose of nitroglycerin and the few observations

Our dosage was selected on the basis that it is a clinical dosage unit and the systemic pressure response to sublingual administration of this dose was comparable to the intravenous response in the two patients so studied

Our observations are consistent with those of Benchimol Desser and Gartlan[9] in which inhaled amyl nitrate and sublingual nitroglycerin resulted in an increase in coronary flow that appears transient but is not quantitated or correlated with arterial pressure

Electromagnetic flowmeter studies in normal dogs reveal a pattern of response to intravenous nitroglycerin that is similar to that in man [12,13] The initial increase in coronary flow is greater

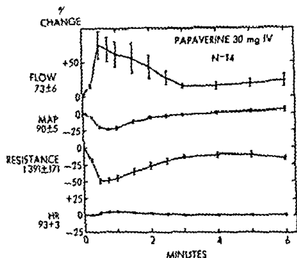


Fig 4 Same as Fig 1 for 14 grafts studied with intravenous papaverine

(35 per cent[13] and 67 per cent[12]) but persists for only 20 seconds and flow then falls below control for two minutes more

Ganz and Marcus[11] have measured coronary sinus flow by continuous thermodilution and found that intracoronary nitroglycerin increases coronary flow 27 to 147 per cent in normal man and 2 to 55 per cent in 14 out of 25 patients with coronary artery disease [11] Coronary sinus flow did not increase in six patients receiving intravenous nitroglycerin Since our flow measurements were in diseased vessels having bypass grafts they may

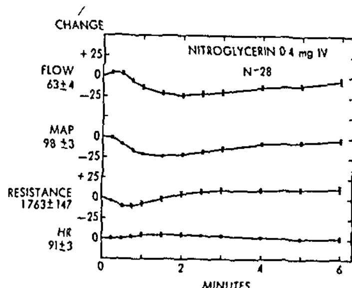


Fig 1 Mean control values ± S E M and mean per cent change from control ± 1 S E M are shown for 28 grafts studied with intravenous nitroglycerin in which graft flow = milliliters per minute mean arterial pressure = MAP coronary vascular resistance = resistance and heart rate = HR

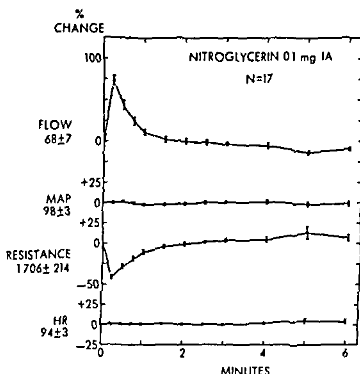


Fig 2 Same as Fig 1 for 17 grafts studied with intra arterial nitroglycerin

Results

The data are summarized in Figs 1 2 4 and 5 in which mean control values ± 1 S E M and the mean per cent change ± 1 S E M from the control values are shown for each time interval

Intravenous nitroglycerin increases coronary flow at 15 (4 ± 1 0 per cent p <0 001) and 30 seconds and then flow falls significantly below control to reach a nadir (23 ± 3 per cent) at two minutes followed by a gradual return to control at five minutes (Fig 1) The mean arterial pressure is unchanged at 15 seconds has begun its decline at 30 seconds (8 ± 1 1 per cent p <0 001), and reaches a low at 90 seconds before returning to control at six minutes Coronary vascular resistance falls in the initial minute (p <0 001) but rises by two minutes (p <0 001) and remains elevated until six minutes Heart rate is significantly elevated from 60 to 180 seconds

The response to sublingual nitroglycerin (0 4 mg) in two of these patients was similar to that following intravenous administration but there was no increase in coronary flow and the duration of diminished coronary flow and arterial pressure was longer (8 to 10 minutes)

Intra arterial nitroglycerin (Fig 2) achieves a peak coronary flow in 15 seconds (74 ± 6 per cent) which returns to control by 90 seconds and then gradually drifts below control at five and six minutes (p <0 05) Although mean arterial pressure declines at five and six minutes this change is not statistically significant nor is the increase in coronary vascular resistance Heart rate is stable

Intra arterial saline produced a distinct increase in coronary flow but of a much lesser magnitude than the nitroglycerin (Fig 3)

Papaverine intravenously (Fig 4) produces a maximal coronary flow at 30 seconds (76 ± 21 per cent) followed by an initial steep decline which levels out at three minutes 15 to 20 per cent above control (p < 0 02) and persists at this level Mean arterial pressure falls maximally at 45 seconds and returns to control by three minutes and there is a 49 ± 4 per cent decline in coronary vascular resistance during this interval Heart rate is significantly elevated from 30 to 120 seconds (p < 0 025)

Intra arterial papaverine (Fig 5) produces a maximal flow response at 45 seconds (215 ± 23 per cent) with a return to control by five minutes There is an associated fall in mean arterial pressure which is maximal at 60 seconds (17 ± 2 per cent, p <0 001) and has returned to control by 150 seconds The fall in coronary vascular resistance is correspondingly great (72 ± 2 per cent) Heart rate is significantly elevated from 45 to 120 seconds

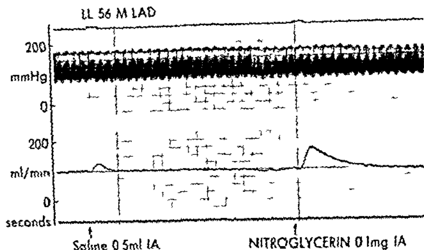


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Discussion

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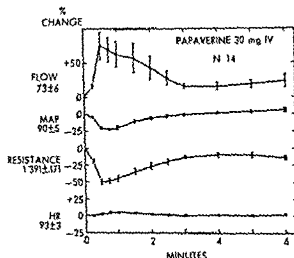


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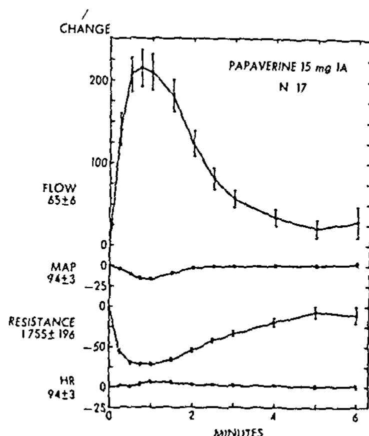


Fig 5 Same as Fig 1 for grafts studied with intra arterial papaverine

be considered to fall into an intermediate group between the normal patients and those with occluded coronaries Their observed flow responses to nitroglycerin are remarkably similar to ours with the exception that they did not observe the 20 second increase in flow after intravenous nitroglycerin

Our observations lend support to the concept that nitroglycerin relieves angina through its effect on the systemic circulation and not via an increase in coronary flow [6 11 16] Even though we observed a transient rise in coronary flow it is unlikely that this small increase would contribute to anginal relief, and it may be absent in those with coronary disease[11] or dependent on intravenous administration [12 13] Furthermore the myocardial distribution of the increased flow is unknown but it is unlikely that it is distributed to areas of need or ischemia [11]

The observations on papaverine have been reported because they offer some basis for comparison with nitroglycerin It is apparent that papaverine in the dose used is a more effective coronary vasodilator and a less effective systemic vasodilator than is nitroglycerin If clinical effectiveness is based in part on an increase in coronary flow then papaverine would warrant greater usage However, its value is limited by lack of a sublingual dosage form The value of oral papaverine in the management of angina pectoris cannot be ascertained from these studies

Summary

Blood flow has been measured in 28 aortocoronary saphenous vein bypass grafts performed for chronic angina pectoris using the electromagnetic flowmeter Nitroglycerin 0 4 mg intravenously or 0 1 mg into the graft and papaverine 30 mg intravenously or 15 mg into the graft were studied Intravenous nitroglycerin increased coronary flow a maximum of 4 per cent for 20 seconds followed by 23 per cent decline as mean arterial pressure fell 23 per cent Intra arterial nitroglycerin increased coronary flow 74 per cent in 15 seconds with return to control by 90 seconds Intravenous papaverine elevated coronary flow 76 per cent at 30 seconds with stabilization of flow 15 to 20 per cent above control Intra arterial papaverine achieves a maximum flow of 215 per cent at 45 seconds with return to control at five minutes Although nitroglycerin produces a small but significant rise in coronary flow it is doubtful whether this increase occurs with oral administration in the presence of coronary disease Thus the therapeutic effect of nitroglycerin lies in its systemic effects rather than in its coronary effect

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Recognition of myocardial infarction after cardiac surgery and its relation to cardiopulmonary bypass

Mohammad Farooq Ghani M D
Brent M Parker, M D *
John R Smith, M D
St Louis Mo

Efforts to allay recurrences of myocardial ischemia or frank infarction have resulted in the *increasing use of coronary artery bypass surgery* By the same token intracardiac surgery has been widely applied to the correction of intracardiac defects and the placement of prosthetic valve devices Both of these surgical maneuvers have required the use of cardiopulmonary bypass support In recent years, however, it has become *increasingly apparent that acute myocardial infarction may appear as a postoperative complication in patients who have undergone coronary bypass or intracardiac procedures under extracorporeal pump control* There is little doubt that these forms of therapy have been notably successful in many patients, nevertheless little attention has been leveled at the ischemic sequellae that may arise to mar the value of the procedure for some patients With these circumstances in mind, our purpose is to compare groups of patients who have undergone cardiac surgery requiring cardiopulmonary bypass procedures, to attempt to identify the factors that *are related to the development of intra or* postoperative myocardial infarction and to assess methods for detection of myocardial infarction in cardiac surgical patients

From the Cardiovascular Division Department of Medicine Washington University School of Medicine and the Barnes and St. Louis City Hospitals St Louis

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Reprint requests to Dr M F Ghani Washington University Medical Service St Louis City Hospital 1515 Lafayette St. Louis Mo 63104

Now Professor of Medicine University of Missouri School of Medicine Columbia

Methods

Ninety nine consecutive patients who were subjected to coronary artery bypass or to open heart surgery comprise the study group Forty eight of these patients had coronary bypass surgery and 51 had open heart surgery for the correction of valvular disease In all of these subjects detailed preoperative observation including cardiac catheterization was performed in those with clinical evidence of coronary disease, the diagnosis was established by coronary angiography Other preoperative investigations included electro and vectorcardiography, serum cholesterol blood uric acid level and enzyme determinations serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) and creatine phosphokinase *(CPK)* In the coronary artery bypass group 11 patients exhibited disease of a single coronary vessel multiple arteries were involved in 37 cases Coronary artery surgery was performed employing a technique similar to that described by Favaloro[1,2] The open heart surgery procedures included the correction of aortic, mitral and tricuspid valvular defects One individual was operated on for an atrial septal defect The patients were placed on conventional cardiopulmonary bypass during the operations Serial 12 lead electrocardiograms were recorded frequently, and enzyme determinations were followed daily for three or more days following the procedure The upper limits of normal for serum enzymes in our laboratories are SGOT, 40 I U per liter LDH 225 I U per liter and CPK 145 I U per liter Vectorcardiograms were available in 74 cases All the subjects were monitored constantly for arrhythmias

and repeatedly examined for evidence of congestive heart failure The diagnosis of transmural acute myocardial infarction was based upon the usual and persistent electrocardiographic QRS wave abnormalities associated with myocardial necrosis

Results

The patients were divided into groups depending on the type of surgery and on whether infarction developed The results are summarized in Table I

Incidence of myocardial infarction in the operated subjects Acute myocardial infarction developed in 21 per cent of the patients with coronary artery bypass surgery and in 14 per cent of those with open heart surgery This difference in numbers is not statistically significant (P> 0 05) The general incidence of myocardial infarction in both groups was 17 per cent Inferior wall infarction comprised 60 per cent of infarcts in the coronary bypass patients and 57 per cent in the open heart surgery group Other locations of the myocardial lesion were anterolateral in 2 anteroseptal in 2 lateral in 2 and posterior in 1 Infarction occurred in 9 of 37 patients receiving multiple vessel bypass grafts compared to 1 of 11 patients undergoing single vessel graft surgery Three subjects had left main coronary arterial obstruction in the bypass group 2 of whom suffered infarction after the surgery Of the patients with open heart surgery there was no predilection for myocardial infarction in any particular cardiac lesion or procedure

Vectorcardiographic studies were available in 13 of the 17 patients with myocardial infarction and added confirmation to the diagnosis in all of the patients so studied. There were no false negatives among the vectorcardiograms

Age and sex There were 7 women and 41 men in the bypass surgery group of patients and 26 women and 25 men in the open heart series No apparent relationship between the patients sex and the development of myocardial infarction was discerned. The average ages in all of the patient groups were similar with the exception of slightly higher ages in those patients suffering myocardial infarction in the open heart surgery group (see Table I)

Arrhythmias and congestive heart failure Neither atrial junctional nor ventricular dysrhythmias, nor congestive heart failure was associated with the occurrence of myocardial infarction in the two groups of patients

Cholesterol and uric acid values The average serum cholesterol level for the coronary artery bypass patients was 254 mg per 100 ml those with open heart surgery had mean levels of cholesterol of 233 mg per 100 ml Those who developed myocardial infarction had somewhat lower mean values of cholesterol None of these differences was statistically significant The serum uric acid levels were similar in the two groups

Cardiopulmonary bypass pump time The cardiopulmonary bypass pump time was longer by 33 per cent in the patients who developed myocardial infarction This difference was statistically significant as analyzed by the Student s t test (P < 0 02)

Serum enzyme levels SGOT LDH and CPK enzyme values were analyzed for significant elevations in those patients sustaining acute myocardial infarction after surgery An elevation of at least two of these enzyme values was noted in patients who developed infarction (P < 0 05) The actual values appear in Table I A stronger correlation was noted at higher cutoff levels

Discussion

This study indicates that acute myocardial infarction may be a frequent complication of cardiac surgery especially in consequence of the use of cardiopulmonary bypass procedures Postoperative electrocardiographic changes diagnostic of acute infarction occurred in 17 per cent of our patients Electrocardiographic analysis constituted the most reliable means of detection of cardiac infarction Vectorcardiography confirmed the diagnosis with no false negative recordings In addition there was a significant correlation with serum enzyme values although elevations occurred without infarction as a result of tissue injury Similar enzyme rises in the course of postoperative infarctions in coronary bypass surgery have been noted by other workers[3,4] Three of our patients died, either during or within several days of operation One patient who died on the operating table during the coronary artery bypass surgery was excluded from the study as no postoperative observations were possible Two persons died following valve replacement surgery Autopsy was permitted in

Table I

	Coronary bypass surgery	Coronary bypass surgery—myocardial infarction	Coronary bypass surgery—nonmyocardial infarction	Open heart surgery	Open heart surgery—myocardial infarction
Total number of patients in each group	48	10 (21%)	38	51	7 (14%)
Age (years)	49 91	50 4	49 42	51 29	55 85
Sex Male	41	8	33	25	4
Sex Female	7	2	5	26	3
Arrhythmia	15	3 (30%)	12 (32%)	26	4 (57%)
Congestive heart failure	10	2 (20%)	8 (21%)	7	2 (29%)
Cholesterol (mg /100 ml)	254	242	266	233	230
Uric acid (mg /100 ml)	6 40	6 44	6 36	6 01	6 08
Cardiopulmonary bypass pump time (in minutes)	139	152	126	139 5	165
Enzyme elevation A	5	4	1	9	6
Enzyme elevation B	15	6	9	25	5

A elevation of at least two enzymes SGOT > 300 LDH > 600 and CPK > 1 200 P < 0 01 for individual groups and total series
B elevation of at least two enzymes SGOT > 200 LDH > 400 and CPK > 800 P < 0 05 for the total series
P < 0 2 (by Student s t test)

one and confirmed the diagnosis of myocardial infarction

There were a variety of abnormal electrocardiographic changes after the surgical procedures other than those indicating myocardial infarction and are not unexpected after cardiac manipulation and injury ST segment and T wave changes were commonly seen after the operation In like manner some elevation of serum enzyme levels was frequently seen undoubtedly as the result of surgery itself [5]

The incidence of myocardial infarction related to the surgical operations was similar in our two groups of patients This relationship suggests that certain common factors may underlie the development of infarction The data indicate that the cardiopulmonary bypass pump time was appreciably longer in those patients who suffered postoperative infarction Quite evidently the incidence of the cardiac accident rises after the more difficult and prolonged operations Other variables such as age sex arrhythmias congestive heart failure serum cholesterol, and uric acid levels did not appear to influence the frequency of subsequent ischemia and infarction In a recent report various risk factors such as a certain age group and elevated cholesterol in patients requiring coronary bypass surgery were studied however, a control group was not used [6] Our study does not show these factors to be characteristic for patients undergoing bypass surgery, or bear a relationship to the development of operative infarction

Certain features relating to the development of myocardial infarction in the coronary bypass patients appear to be important. These in

Open heart surgery—nonmyocardial infarction	*Total series*	
	Myocardial infarction	*Nonmyocardial infarction*
44	17 (17%)	82
50 56	53 12	49 99
21	12	54
23	5	28
22 (50%)	7 (41%)	34 (41%)
5 (11%)	4 (24%)	13 (16%)
236	236	251
5 97	6 26	6 16
114	159 5	120
3	10	4
20	11	29

dividuals usually exhibited generalized disease of the coronary arteries on angiography Two of the three patients with left main coronary arterial obstruction suffered cardiac infarction one anteroseptal and the other posterior in location. Only one of the 11 patients receiving single vessel bypass developed infarction as compared to 9 of 37 patients undergoing multiple vessel bypasses Postoperative infarction therefore appears to occur more commonly in patients with generalized disease of the coronary vasculature requiring a larger number of bypass grafts Furthermore the left main coronary artery may be a critical site of obstruction in relation to the postoperative events described here [7]

The location of the postoperative infarcts was not necessarily related to the artery that was surgically bypassed and the operative sites of the ventricles In like manner the site or form of valvular replacement bore little relation to the site of the myocardial ischemia The most common location of the intruding infarcts in our cases was in the inferior myocardium An explanation for this phenomenon is not readily apparent However it seems possible that following manipulation of the heart muscle and the grafting in of artificial vascular conduits there may be a decline of net coronary inflow interfering with the flow in opened collateral vasculature especially in the regions of termini of the right and left circumflex coronary arteries Inferior ischemia or frank infarction of the muscle may then ensue For example it has been shown in the pulmonary circulation that embolism may lead to opening of collateral vessels however if net flows are insufficient the open collateral vasculature fails to prevent the development of infarction within the tissue [8] It seems logical that the same may obtain for the myocardium

At the present time the principal benefit of coronary artery bypass grafting appears to be the relief of chest pain [9,10] Previous experience by many observers has emphasized the value of caution in the interpretation of therapeutic results that depend primarily upon subjective evaluation After operations involving thoracotomy and bilateral internal mammary artery ligations the amelioration of angina pectoris may be as high as in 95 per cent of patients [11] Indeed, there is also the suggestion that myocardial infarction following coronary surgery may prompt the relief of anginal pain [3,12]

It is patently evident that myocardial infarction induced by cardiac surgery may increase postoperative mortality and morbidity and may also adversely affect the competence of the heart at a later date Therefore identification of the factors related to the development of operative myocardial infarction is of extraordinary importance if the complication is to be avoided. In sum diffuse coronary artery disease requiring multiple bypasses lesions of the left main coronary artery or operative procedures necessitating prolonged maintenance of patients on the cardiopulmonary bypass pump seem to predispose to myocardial infarction after surgery It is hoped that improved classification of patients in terms of these surgical risks together with improved techniques related to these procedures will lessen the incidence of disastrous postoperative

complications and subsequent continued disability of the heart

Summary

The incidence of operatively related acute myocardial infarction in patients undergoing coronary artery bypass surgery and open heart surgery was determined and compared Elevation of at least two enzymes, SGOT > 200 LDH > 400 and CPK > 800 was noted in patients with myocardial infarction (P < 0 05) The overall incidence of infarction was 17 per cent and there was no significant difference in frequency of infarction in the two groups Inferior myocardial infarction was the most common locus of damage All patients developing myocardial infarction in the coronary bypass surgery group had evidence of generalized coronary artery disease Infarction most frequently developed in patients requiring multiple vessel bypasses Lesions of the left main coronary artery seem to be critical The cardiopulmonary bypass pump time was 33 per cent longer in patients sustaining myocardial infarction a statistically significant difference (P < 0 02) Age sex arrhythmias congestive heart failure serum cholesterol or uric acid levels appeared not to be related to the development of postsurgical myocardial infarction in these cases These data indicate that myocardial infarction is common both after coronary bypass surgery and open heart surgery and that the incidence rises with the more difficult and longer operations

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Aortic valve replacement One-year results with Lillehei Kaster and Bjork-Shiley disc prosthesis

A comparative clinical study

Sigurd Nitter Hauge M D
Karl Victor Hall, M D
Tor Froysaker M D
Leif Efskind, M D
Oslo Norway

The hemodynamic and functional advantages reported with the new Lillehei Kaster pivoting disc valve and the Bjork Shiley tilting disc valve prosthesis in patients with aortic valve disease have been encouraging although the follow up has not been long [1-4] Data from a clinical trial permitting a direct comparison between long term results with the two types of these new prostheses have also been lacking but should be of considerable interest For the latter purpose we have used the two disc prostheses in a randomized study in the years 1971 and 1972 inserting one of them alternatively in patients with aortic valvular disease This report deals with our clinical results in the first 68 patients re examined 12 months after the operation

Material and methods

The present study includes 68 patients with aortic stenosis and/or insufficiency who underwent operation with disc valve replacement in the period from 1971 to 1972 In most patients the valvular lesions appeared to be of rheumatic or congenital origin In a few patients there was a history of acute or subacute bacterial endocarditis. Associated mitral valve disease was observed in 19 patients, but none of them were treated with concomitant mitral valve surgery There were 54 men and 14 women

Prior to operation the patients were randomized and a Lillehei Kaster or a Bjork Shiley (Delrin) disc prosthesis was inserted alternatively Table I shows that preoperatively the average age average heart volume distribution of cases with various types of aortic valve lesions and distribution of cases with various grades of functional disability were the same in the two groups of patients

The aortic valve was approached through a midsternal incision Total cardiopulmonary bypass with hemodilution and mild hypothermia was employed, and the left coronary artery perfused continuously in all patients Anticoagulation therapy with warfarin was given routinely postoperatively

The follow up ranged from 12 to 15 months and the follow up information was obtained by re admitting the patients to hospital for about one week s stay They were carefully investigated by clinical examination The functional capacity limited by angina pectoris or dyspnea preoperatively as well as at the time of the re examination was established in personal interviews. The patients were grouped in four classes (I through IV) for functional cardiac capacity according to the criteria defined by the New York Heart Association [5] Almost all patients underwent cardiac catheterization with aortography while transseptal catheterization was not done Aortic regurgitation was assessed semiquantitatively and was classified as follows *none or slight moderate and severe* Radiologic heart size was determined in all cases

From Medic l Department B nd Surgical D partment A Uni ers ty Hospital, Rikshospitalet, O lo Norway

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Reprint requests to Sigurd Nitte Haug Medical Department B, Un ersity Hosp tal, R kshospitalet, Oslo 1 Norway

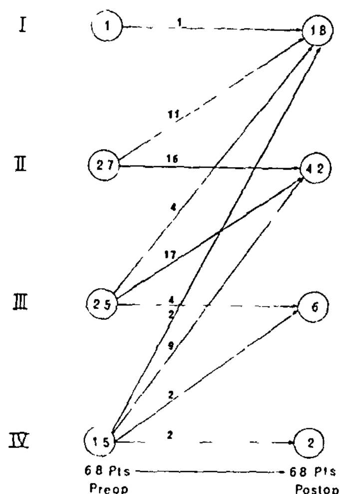


Fig 1 The functional improvement experienced by the survivors of aortic valve replacement One year s results with a Lillehei Kaster pivoting disc valve or a Björk Shiley tilting disc valve

The statistical significance between pre and postoperative findings as well as differences between the two groups of patients was tested by Student s t test [6] P values higher than 0 05 were not considered to be significant

Results

Subjective improvement A comparison between functional cardiac capacity immediately before the operation and one year after the operation is given in Fig 1 Symptomatically most of the patients experienced definite improvement (Classes I and II according to the N Y H A classification) *Of the 68 patients re examined* a total of 45 or 67 per cent considered themselves in a better condition than before operation Eighteen patients were free of symptoms (26 per cent) and another 42 patients (62 per cent) had only minor complaints of cardiac symptoms *present as dyspnea or angina* pectoris on exertion (N Y H A Classes I and II) A total of 8 *patients or 12 per cent* were still markedly incapacitated (N Y H A Classes III and IV) There *was no difference in functional* improvement between patients with a Lillehei Kaster *prosthesis compared to those with a* Björk Shiley prosthesis (Table II) Although a definite *symptomatic improvement was registered* in most of the patients with additional *mitral disease five of the 19 patients in this* subgroup were in functional Classes III and IV (N Y H A) *one year after the operation*

Radiologic heart volume Radiologic heart volume *before and 12 months after operation* was available in all but three patients A com*parison between data from these two examina*tions is given in Fig 2 Most cases with pure aor*tic disease showed a slight to definite decline in* heart volume following operation In these pa*tients mean heart volume following insertion of* the Lillehei Kaster prosthesis was reduced from *680 to 584 ml per square meter of body surface* area and after insertion of a Bjork Shiley pros*thesis from 605 to 502 ml per square meter* of body surface area Both these reductions were *significant* ($0\ 01 > p > 0\ 001$) *In contrast the small group of patients with mitral disease in ad*dition had in general unchanged heart volume values upon re examination In the group with the Lillehei Kaster prosthesis mean heart volume before operation was 711 ml per square meter of body surface area versus 678 ml per square meter of body surface area at the one year examination and corresponding values after insertion with a Bjork Shiley prosthesis were 692 ml per square meter of body surface area and 780 ml per square meter of body surface area The difference between pre and postoperative values were statistically not significant ($p > 0\ 05$)

Left ventricular hypertrophy In 34 patients with pure aortic disease it was possible to evaluate the functional results by measuring the combined voltage in precordial leads before and one year after the operation The remaining 15 pa*tients with pure aortic disease had either a right* or left bundle branch block or pacemaker The *results are shown in Fig 3* The combined voltage of $SV_1 + RV_5$ decreased distinctly from a mean *value of 53 mm* to 36 mm in patients with a Lillehei Kaster prosthesis and from 49 mm to 34

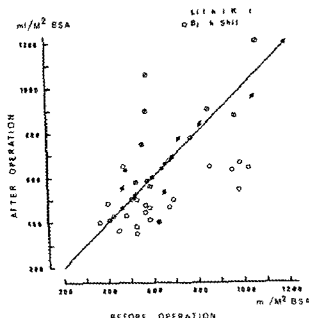


Fig 2. Radiologic heart volume before and one year after single aortic valve replacement Patients with additional mitral valvular disease are marked with a dash

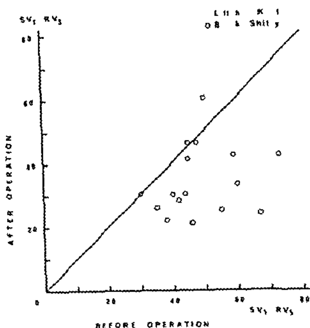


Fig 3 Comparison between combined voltage of $SV_1 + RV_5$ before and one year after single aortic valve replacement

Table I Comparison between preoperative findings in two randomized groups of patients

Type of prostheses inserted	*Average age (yrs)*	*Average heart volume (mL/M²BSA)*	*Type of valve lesion*				*N Y H A classification*			
			AS	*AI*	*AS + AI*	*AS/AI + Mitr*	*I*	*II*	*III*	*IV*
Lillehei Kaster (n = 33)	52 4 (36 64)	697 (435 1 200)	1	13	10	9	1	14	13	5
Björk Shiley (n = 35)	51 5 (15 67)	634 (350 1 070)	5	7	13	10	0	13	12	10

mm. in patients with a Bjork Shiley prosthesis For both groups the reduction in combined voltage in precordial leads was statistically significant (p < 0 001)

Valvular regurgitation Follow up aortography was done in 59 patients, and was omitted in 9 patients. This was mainly due to reluctance of the patients to be subjected to another catheterization while they were feeling well Regurgitation at follow up aortography was classified as in Table III It is evident that patients with a Björk Shiley prosthesis showed somewhat greater valvular regurgitation than patients with a Lillehei Kaster prosthesis but in both groups the number of patients with more severe insufficiency was small None of the patients had to be operated upon The incidence of paravalvular leakage was higher in patients with a Bjork Shiley prosthesis than in those with a Lillehei Kaster prosthesis The paravalvular leaks ranged from small to more massive but were usually small fistulas and only one patient had to be reoperated upon

Discussion

Aortic valve replacement has become a well established procedure in the treatment of patients with aortic valve disease, and results from follow up studies of large series have been reported over the past years Most studies in this field, however have been based on examinations

Table II The functional improvement experienced by survivors of aortic valve replacement in a comparative study between Lillehei Kaster and Björk Shiley disc prostheses Figures in brackets refer to patients with mitral valve disease in addition

N Y H A classification	*Lillehei Kaster*		*Bjork-Shiley*	
	Preoperative	*Postoperative*	*Preoperative*	*Postoperative*
I	1(0)	9(2)	0	9(2)
II	14(1)	20(5)	13(1)	22(5)
III	13(5)	3(1)	12(6)	3(2)
IV	5(3)	1(1)	10(3)	1(1)

Table III Results of follow up aortography following replacement with Lillehei Kaster or Bjork Shiley aortic disc valve prosthesis

Classification of regurgitation	*Type of prostheses*	
	Lillehei Kaster (n = 27)	*Björk-Shiley (n = 32)*
None or slight	24	16
Moderate	2	14
Severe	1	2
Paravalvular	4	7

of patients with ball valve prostheses of different construction while informative data regarding the long term results after insertion of the new disc valve prothesis are more scanty This is particularly true when discussing the new Lillehei Kaster prosthesis In the present study a total of 68 patients have been re examined one year after single aortic valve replacement with either the Lillehei Kaster pivoting disc prosthesis or the Bjork Shiley tilting disc prosthesis The patients were randomized prior to operation and one of these two disc prostheses was inserted alternatively

The results showed that the majority of patients had experienced a marked clinical improvement with relief of symptoms (up one or two functional classes according to N Y H A) Nearly 90 per cent of the patients were either asymptomatic and able to live a normal physical life or had mild dyspnea on effort (N Y H A Classes I and II) The good results obtained in the patient group with the Björk Shiley prosthesis are in accordance with other recently published follow up studies with this prosthesis Both Björk, Olin, and Rodriguez[2] as well as Fernandez and associates[3] have reported that approximately 90 per cent of their patients were either in excellent condition free of symptoms or experienced mild dyspnea on effort, and less than 10 per cent complained of shortness of breath or (in a few cases) signs of congestive heart failure In a third study Messmer and co workers[4] stated that one or two years after operation 71 per cent of the patients with a Björk Shiley tilting disc valve prosthesis were in Classes I or II (N Y H A) The functional status after insertion of a Lillehei Kaster pivoting disc valve is less well known Our results indicate that the clinical improvement following replacement with the aforementioned prosthesis is just as good as with the Bjork Shiley prosthesis used in the present study The good functional results following replacement with either of the two prostheses are supported by the finding of a decrease in heart volume and a decrease in voltage in precordial leads

The results from the follow up evaluation of a small number of patients who had mitral valve disease in addition to aortic valve disease should

be commented upon more closely The mitral valve disease in these patients was thought to be of little hemodynamic significance not necessitating surgical correction The postoperative evaluation showed that, irrespective of which of the two types of prostheses had been inserted, the functional improvement in this group was less obvious than in patients with pure aortic stenosis and that the heart volume in general had remained unchanged The lesser reduction in heart volume seen in this subgroup compared to that in patients with pure aortic disease may be due to the fact that patients with mitral valve disease have impairment of myocardial function due to a low output state atrial fibrillation pulmonary vascular disease and tricuspid valvular disease [7] These factors will persist after single aortic valve replacement and might have been responsible for the persistence of the cardiac enlargement

Based on findings at aortography we found that the regurgitation through the Björk Shiley prosthesis was greater than in patients with a Lillehei Kaster prosthesis Most probably the reason for this observation is that the former prosthesis does not occlude the ring during diastole while the backflow with the Lillehei Kaster prosthesis is minimal For both types of prostheses however the amount of aortic regurgitation seen in the aortograms was considered to be mild or moderate In the present study we were not able to demonstrate that this difference in prosthesis design was of any importance for the symptomatic improvement and functional status seen one year after the operation The functional improvement experienced by the survivors in the present study does not seem to differ from results achieved in a large series of patients after successful insertion of other types of prostheses [8] Thus the introduction of these new types of aortic valve prostheses does not seem to influence late functional results This is illustrated by the fact that our results do not differ from the results in a similar clinical evaluation of a large group of patients following replacement with single aortic ball valve prostheses published from this hospital by Storstein and Efskind [9] However it should be added that patients with the two types of disc prostheses distinguish themselves from patients with ball valves by having a definite lesser incidence of hemolysis as shown by us in a recent study [10] It has also been claimed that the patients with the new disc valves should be less inclined to late thromboembolic complications than patients with an aortic ball valve prosthesis So far no thromboembolic episodes have been observed in the present series but the follow up period is too short to reach final conclusions

Summary

The present study presents clinical and functional results obtained in a randomized series of 68 patients examined one year after single aortic valve replacement with either a Lillehei Kaster pivoting disc valve or a Björk Shiley tilting disc valve Symptomatic improvement was experienced in 67 per cent of all patients re examined, and 88 per cent were in functional Classes I and II In patients with pure aortic valve disease heart volume was significantly reduced while a small group of patients with mitral valve disease in addition had unchanged or slightly increased heart volume Regression of left ventricular hypertrophy in the electrocardiogram was also noted in most patients It is felt that the clinical and functional results may be of the same order of magnitude in patients with the Lillehei Kaster model as in patients with the Björk Shiley prosthesis

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An analysis of the left ventricular response to isometric exercise

Miquel A Quinones M D
William H Gaasch M D
Efrain Waisser M D
Hans G Thiel M D
James K Alexander M D
Houston, Texas

In studies of the left ventricular response to isometric exercise conventional ventricular function curves have been utilized to separate patients with diminished cardiac reserve from those with adequate reserve Patients with left ventricular dysfunction have been shown to develop little or no increase in left ventricular stroke work during isometric exercise in spite of marked increases in left ventricular end diastolic pressure patients with normal left ventricular reserve develop significant increases in stroke work with minor changes in end diastolic pressure [1,3] This response suggests that during isometric exercise the normal left ventricle increases its contractile state and shifts to an augmented ventricular function curve while the ventricle with a poor myocardial reserve may fail to do so The purpose of this study was to further define the mechanism of the normal as well as the abnormal response to isometric exercise and to evaluate the usefulness of this type of exercise as a stress test for inducing abnormalities of left ventricular function in a group of patients with resting hemodynamics ranging from normal to clearly abnormal

Methods

Twenty nine patients were studied during routine diagnostic cardiac catheterization performed in the postabsorptive state following premedication with 10 mg of intramuscular Diazepam Informed consent was obtained from every patient Right and left heart catheterization a resting cardiac output determination using the Fick principle for oxygen left ventricular cineangiography (60 frames per second) and coronary angiography were performed in all patients. Systolic ejection fraction was derived by the method of Greene and co workers [4] There were 12 patients with normal left ventricular hemodynamics at rest and normal coronary arteries 14 patients with coronary artery disease (CAD) two patients with rheumatic valvular disease and one patient with idiopathic congestive cardiomyopathy Isometric exercise was performed using a hand grip dynamometer (Jamar dynamometer) Measurements were made at rest and at three minutes of sustained hand grip at 25 per cent of maximum voluntary contraction A normal ventilatory pattern was observed in each patient throughout the test period Arterial blood pressure was measured percutaneously from the left brachial or radial artery utilizing a Statham P 23Db strain gauge transducer Left ventricular (LV) pressure and the electronic differentiation of the pressure (dP/dt) were recorded in 27 patients with a catheter tip micromanometer (Millar Instruments Inc) A multichannel recorder with paper moving at 200 mm per second was utilized (Electronics for Medicine) Force velocity relations were calculated in these patients at rest and during isometric exercise by analysis of left ventricular pressure and dP/dt at 10 msec intervals Contractile element velocity (V_{CE}) was calculated using both total as well as developed LV pressure The following for

From the Department of Medicine Baylor College of Medicine and Ben Taub General Hospital, Houston

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Reprint requests to Dr William H. Gaasch, Department of Medicine Cardiology Division, Baylor College of Medicine 1200 Moursund Ave Houston, Te 7 0 5

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Max dP/dt (mm. Hg/sec) C	Max dP/dt (mm. Hg/sec) IE	Peak V_{ce} (1/sec) C	Peak V_{ce} (1/sec) IE	V_{max} (1/sec) C	V_{max} (1/sec) IE	(dP/dt)/40 (1/sec) C	(dP/dt)/40 (1/sec) IE	V_{ce} DP 10 (1/sec.) C	V_{ce} DP 10 (1/sec.) IE	SEF (%)	Diagnosis
1 436	1 738	1 49	1 70	1 89	2 20	32 0	37 0	2 58	3 10	67	
126	148	0 08	0 06	0 09	0 08	2 6	2 5	0 19	0 23	3	
<0 01		<0 01		<0 01		<0 01		<0 01			
1 500	1 650	1 50	1 40	1 90	2 00	38	39	2 90	3 00	50	CAD
1 320	1 890	0 90	1 00	1 00	1 20	36	45	3 20	3 80	42	CAD
1 300	1 500	0 85	0 75	1 00	1 00	30	34	2 58	2 84	35	CAD
1 080	1 200	1 00	1 00	1 50	1 60	30	32	2 63	2 9?	50	CAD
—	—	—	—	—	—	—	—	—	—	60	CAD
1 ?40	1 350	1 40	1 00	1 70	1 30	30	31	2 50	2 50	71	CAD
—	—	—	—	—	—	—	—	—	—	29	CAD
710	1 090	0 52	0 59	0 84	0 76	18	26	1 50	1 50	23	CC
710	860	0 50	0 40	0 55	0 45	19	19	1 54	1 54	30	RHD
2 360	2 930	1 20	1 20	1 60	1 60	39	42	2 16	1 83	71	RHD
12 8	1 559	0 98	0 92	1 26	1 24	30	33	2 34	2 49	46	
165	227	0 13	0 10	0 17	0 18	3	3	0 22	0 29	5	
<0 01		NS		NS		<0 05		NS			
8	8	8	8	8	8	8	8	8	8	10	
1 650	2 160	1 50	1 60	1 80	2 10	36	46	3 08	3 75	53	CAD
1 520	1 652	1 60	1 60	2 20	2 ?0	33	35	2 62	2 62	70	CAD
1 380	1 446	1 50	1 50	2 10	2 10	30	30	2 60	2 60	77	CAD
1 205	1 352	1 50	1 50	1 90	1 95	28	29	2 80	2 80	52	CAD
1 440	1 600	1 07	1 10	1 20	1 25	28	30	2 16	2 16	56	CAD
14 9	1 642	1 84	1 94	1 43	1 46	31	34	2 65	2 78	62	
?4	140	0 17	0 18	0 09	0 09	1 5	3	0 15	0 26	5	

SWI st ke work index SEF = systolic ejection f a tion CAD = c ronary artery disease CC cong t e di myop thy RHD rheumat valvu

patients were studied during atrial pacing at a heart rate equal to the one achieved during exercise In addition five patients were studied during isometric exercise with heart rate held constant by atrial pacing

A paired t test was used for statistical analysis of the data

Results

The patients were divided into three groups depending on their response to isometric exercise (Table I) Group I consisted of nine patients (eight with normal coronary arteries and one with triple vessel coronary artery disease) all responded to hand grip with a significant increase in LVSWI associated with only a minimal rise in LVEDP (3 mm Hg or less) All patients in this group had normal hemodynamics systolic ejection fractions and force velocity relations at rest They all showed significant increases in LV developed pressure during isometric exercise while maintaining stroke volume Likewise a significant increase in the isovolumic indices of contractility was observed, indicating a shift toward an augmented ventricular function curve during hand grip To test whether the increase in left ventricular contractility observed during isometric exercise was related to the significant increase in heart rate eight of the above patients had measurements of the isovolumic indices made during atrial pacing at a heart rate equal to the one achieved during exercise (Fig 1) Atrial pacing was associated with a significant (p<0 05) increase in all of the indices of contractility however the levels of max dP/dt, V_{max} and (dP/dt)/40 achieved with atrial pacing were sig

Table I Hemodynamic data

	Heart rate (beats/min.)		Mean BP (mm Hg)		LV DP (mm. Hg)		LVEDP (mm. Hg)		Stroke index (c c /beat/m.²)		LVSWI (g m /beat/m.²)	
	C	IE	C	IE	C	IE	C	IE	C	IE	C	IE
Group I												
Average	74	85	89	106	110	134	7	9	43	44	59	73
S E M	5	5	4	5	5	7	1	1	3	3	5	6
p					<0 01				NS		<0 01	
n = 9												
Group II												
1) 54/M	68	80	82	94	98	104	12	21	43	40	53	52
2) 38/M	72	95	85	102	78	92	32	36	61	51	55	58
3) 48/M	72	80	112	123	128	126	22	40	35	33	52	52
4) 54/M	88	104	78	91	102	106	16	21	33	26	41	35
5) 56/M	74	115	120	145	151	140	24	45	34	20	58	28
6) 52/M	63	84	84	122	106	151	9	18	49	—	—	—
7) 53/M	68	88	102	115	102	103	30	45	32	26	39	33
8) 37/M	80	96	68	90	62	77	28	33	29	24	22	22
9) 35/M	88	103	85	95	80	80	25	35	16	—	—	—
10) 34/M	90	112	120	144	135	146	15	24	44	—	—	—
Average	76	96	94	112	104	113	21	32	38	31	46	40
S E M	3	4	6	7	9	9	3	3	4	4	5	5
p												
n	10	10	10	10	10	10	10	10	10	7	7	7
Group III												
11) 54/F	96	112	92	108	113	131	13	14	31	22	43	35
12) 62/F	94	100	100	136	145	176	5	9	35	27	60	55
13) 55/M	60	72	85	101	109	130	6	10	49	39	65	62
14) 55/M	95	100	91	106	122	134	4	6	27	26	39	42
15) 65/F	69	75	103	118	129	152	9	13	47	—	—	—
Average	83	92	94	114	124	144	7	10	38	29	52	49
S E M	8	8	3	6	6	9	2	1	4	4	6	6

C = control IE = isometric exercise BP = systemic blood pressure LV = left ventricular DP = developed pressure EDP = end diastolic pressure
lar heart disease S E M = standard error of the mean

mula was utilized for both methods $V_{CE} = (dP/dt)/kP$ where P = LV pressure, and k = the normalized modulus of series elasticity (24)[5] Peak V_{CE} was measured directly from the total pressure velocity curve and the maximum contractile element velocity at zero load (V_{max}) was derived by linear extrapolation of the same curve to zero pressure Since velocity at zero load (developed pressure) is infinite V_{CE} at a developed pressure of 10 mm Hg (V_{CE} DP 10) was measured as an approximation of V_{CE} at zero lead In addition, the ratio of dP/dt to a common isovolumic pressure of 40 mm Hg, [(dP/dt)/40] was determined[6] In two patients, a fluid filled catheter connected to a Statham P 23Db strain gauge transducer was utilized for recordings of LV pressure In these two cases pressure velocity data were not calculated.

Cardiac output before and at three minutes of isometric exercise was determined by the indocyanine green indicator dilution technique in 20 patients Left ventricular stroke work index (LVSWI in gram meters per beat per square meter of body surface area) was calculated as follows

$$LVSWI = (LV_{sm} \quad LVEDP) \times SI \times 1\ 36/100$$

where LV_{sm} = left ventricular systolic mean pressure LVEDP = left ventricular end diastolic pressure and SI = stroke index (c.c /beat/m ²) Modified left ventricular function curves (LVEDP vs LVSWI) were constructed in the above 20 patients using data obtained prior to and during isometric excercise

In order to assess the contribution of changes in heart rate to the changes in the contractility indices observed during isometric exercise eight

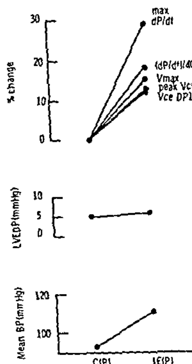


Fig. 2. An example (patient No 3 Table II) of the response to isometric exercise with heart rate held constant (atrial pacing) During exercise mean arterial blood pressure increased there was little change in LVEDP and the isovolumic indices of contractility were augmented (see text) Abbreviations C(P) = control paced, IE(P) = isometric exercise paced.

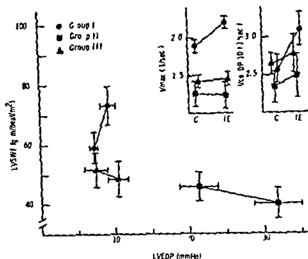


Fig 3 Ventricular function curves from the three groups of patients were constructed from resting (C) and exercise (IE) data In the panels on the upper right V_{max} and V_{CE} DP 10 are also shown. In contrast to Groups II and III the patients in Group I showed improvement in both contractility and in pump function.

will lead to a reduction in myocardial shortening which in turn will decrease the ejection fraction and stroke volume The data from this and other studies indicate that during isometric exercise the normal left ventricle is able to maintain stroke volume while increasing the amount of developed pressure with only minor alterations in end diastolic pressure These data suggest a shift toward an augmented ventricular function curve This concept is strengthened by the finding of an improvement in the contractile state during hand grip similar increases in the isovolumic indices have been observed in previous studies [7,8] However it should be re emphasized that the normal ventricle makes use of some increase in preload during isometric exercise as shown by the minor elevation in LVEDP in spite of the increased heart rate this situation is analagous to the increase in myocardial segment length during dynamic exercise at constant heart rate as shown by Braunwald and co workers [10]

Since increases in heart rate have been shown to produce improvement in left ventricular contractility (treppe or Bowditch effect) [11,15] it would seem reasonable to postulate that the improvement in contractility measured during isometric exercise might be secondary or in part related to the increase in heart rate To test this hypothesis isovolumic indices of contractility were measured in eight patients from Group I during atrial pacing at a rate equal to the one achieved during isometric exercise Isometric exercise was associated with a higher level of myocardial contractility than atrial pacing (see Results) In addition a significant improvement in all of the isovolumic indices of contractility was seen in four out of five patients subjected to isometric exercise at a constant heart rate Thus it seems that in addition to the treppe effect other factors independent of heart rate are involved in augmenting myocardial contractility during isometric exercise

In contrast to a normal heart during isometric exercise a ventricle with a poor myocardial reserve may be unable to increase its contractile state sufficiently to maintain an adequate stroke volume without making use of a significant increase in preload. No significant improvement in the isovolumic indices of contractility was noted in the majority of the patients in Group II during isometric exercise and in spite of significant increases in preload stroke volume fell and left

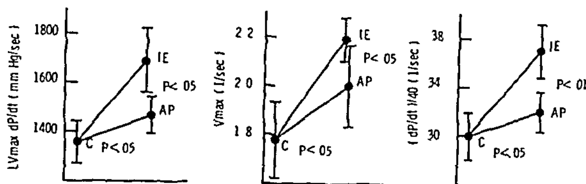


Fig 1 Eight patients with normal LV function were studied at rest (C) during isometric exercise (IE) and during atrial pacing (AP) at a rate equal to that achieved during exercise Both atrial pacing and isometric exercise were associated with increases in LV max dP/dt V_{max} and (dP/dt)/40 the levels achieved during exercise were significantly higher than those measured during pacing

nificantly lower ($p<0.05$) than those achieved during isometric exercise Although the mean values for peak V_{CF} and V_{CF} DP 10 during atrial pacing were lower than during isometric exer cise the differences did not achieve statistical significance Five additional patients (four with normal coronary arteries and one with single vessel CAD) who responded to isometric exercise with a normal increase in contractility, were sub jected to hand grip exercise while heart rate was held constant by atrial pacing (Table II) Mean arterial blood pressure increased in all five pa tients while the measured indices of contractility increased in four patients Fig 2 shows the data from one of these patients Thus the augmented indices of contractility determined in the normal left ventricle during isometric exercise may at least in part be related to the increase in heart rate however factors independent of the fre quency of contraction also appear to be opera tive

Group II consisted of ten patients who re sponded to isometric exercise with an elevation in LVEDP of 4 mm Hg or greater (range 4 to 21 mm Hg) Seven of these patients had ventricular function curves constructed and showed little change or a reduction in LVSWI Although some of the patients had a normal increase in LV de veloped pressure during exercise the mean value for the group during hand grip was not signifi cantly higher than at rest Isovolumic indices of contractility were measured in eight of these pa tients An increase in max dP/dt comparable to the one seen in Group I was observed in this group This increase in max dP/dt apparently re flects the increase in preload occurring during isometric exercise little change in left ventricu lar contractility as measured by the pressure velocity relations was observed in most of these patients (Table I) Of the ten patients in this group seven had coronary artery disease four of whom had systolic ejection fractions of 50 per cent or greater, two of these four patients (Nos 1 and 6) also had values for the isovolumic indices of contractility at rest, comparable to those in Group I

Group III consisted of five patients who re sponded to isometric exercise with changes in heart rate developed pressure and LVEDP com parable to those in Group I In four patients ventricular function curves were constructed and no significant increase in LVSWI was ob served Stroke volume decreased in three pa tients All five patients had coronary artery dis ease with a systolic ejection fraction at rest of 50 per cent or greater Four of them also had normal pressure velocity relations at rest However all except one (No 11) failed to show a significant increase in contractility during isometric exer cise

Fig 3 represents a summary of the response to isometric exercise in the three groups of patients No complications were observed during isometric exercise in any of the patients tested Only one patient (No 6) complained of angina during hand grip Other than infrequent premature ventricular contractions no arrhythmias were observed during the test

Discussion

During isometric exercise left ventricular afterload increases Unless preload is increased appropriately or myocardial contractility is im proved the increase in wall stress during ejection

which this occurred is not entirely clear In patients with CAD one may postulate that the increase in myocardial oxygen consumption produced by the changes in heart rate wall tension and contractility may be sufficient to produce myocardial ischemia which in turn leads to segmental or diffuse left ventricular dysfunction Using left ventriculograms obtained during isometric exercise Flessas and co workers[16] have shown development of hypokinetic areas and reduction in the ejection fraction in patients with coronary artery disease who also had abnormal elevation of the LVEDP during exercise Although myocardial ischemia may play a major role in precipitating left ventricular dysfunction the development of angina during hand grip was a rare occurrence in this study Only one patient (No 6) complained of chest pain during the performance of the test Other than infrequent premature ventricular contractions arrhythmias were not observed in our patients during the period of isometric exercise

In two patients with CAD and disorders of regional contractions (Nos 2 and 11) pump function was depressed during isometric exercise while the pressure velocity relations improved This discrepancy between left ventricular pump function and the isovolumic indices of left ventricular contractility have been previously described In the presence of an acute myocardial infarction normal pressure velocity relations have been reported in spite of reduced left ventricular pump function[17] Thus it seems that in the presence of coronary artery disea e with segmental left ventricular dysfunction the isovolumic indices of contractility may at times reflect the performance of the normal segments of myocardium

Summary

Analysis of the left ventricular response to isometric exercise was performed in a group of patients undergoing diagnostic cardiac catheterization A normal response was observed in nine patients with normal resting hemodynamics (Group I) This response consisted of a significant increase in LV stroke work associated with minor changes (average increase of 2 mm Hg) in LV end diastolic pressure Significant increases were consistently observed in the isovolumic indices of myocardial contractility These findings indicate that the normal left ventricle responds to this form of exercise by improving its contractile state and to a minor degree by increasing preload thus maintaining a constant stroke volume in the presence of an increased afterload

To test whether the increase in contractility observed during isometric exercise was related to the increase in heart rate isovolumic indices of contractility were measured in eight patients during atrial pacing at a rate equal to that achieved during exercise Isometric exercise was associated with a higher level of myocardial contractility than atrial pacing In addition a significant improvement in the isovolumic indices was observed in four out of five patients subjected to isometric exercise at a constant heart rate (atrial pacing) Thus it seems that in addition to the treppe effect other factors independent of heart rate are involved in augmenting myocardial contractility during isometric exercise

Ten patients (Group II) responded to exercise with a marked increase in LVEDP but little change in LV stroke work five patients (Group III) responded with only a minor change in LVEDP (similar to Group I) but with *no improvement* in LV stroke work Myocardial contractility also failed to increase in most of these patients Isometric exercise uncovered abnormalities of LV performance not identified by the resting hemodynamics in a significant number of patients

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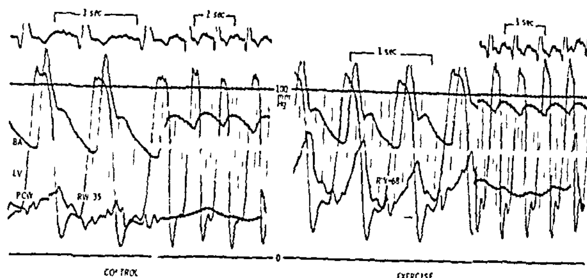


Fig 4 Left ventricular (LV) arterial (BA) and pulmonary capillary wedge (PCW) pressures prior to and during isometric exercise in a patient with chronic mitral regurgitation Note the striking increase in the regurgitant wave (RW) during exercise

Table II Hemodynamic data in five patients performing isometric exercise at constant heart rate (Atrial pacing)

	Dx	Heart rate (beats/min)	*Mean BP (mm Hg)*		*Maximum dP/dt (mm Hg/sec)*		*Peak V_{CE} (1/sec)*		*V_{max} (1/sec)*		*(dP/dt)/40 (1/sec)*		*V_{CE} DP 10 (1/sec)*	
			C	IE	C	IE	C	IE	C	IE	C	IE	C	IE
49/F	N	88	110	122	1 600	1 900	1 42	1 85	1 90	2 40	33	39	2 54	3 38
39/F	N	78	113	129	1 470	1 920	1 45	1 60	1 90	2 20	31	38	2 55	3 00
19/M	N	105	93	110	2 020	2 600	1 60	1 80	2 00	2 30	39	46	2 40	2 70
44/M	N	110	118	122	1 900	2 000	2 20	2 20	2 70	2 70	41	41	3 30	3 30
36/M	CAD	95	116	130	1 490	2 000	1 40	1 53	1 83	2 00	33	42	3 10	3 60

Dx = diagnosis N = normal The other abbreviations are as in Table I

ventricular stroke work failed to improve Although the degree of mean arterial pressure elevation measured during exercise in this group was comparable to the one in Group I no significant increase in left ventricular developed pressure was observed in many of these patients Thus it seems that ventricles with a poor myocardial reserve may not only show inadequate shortening but may also be unable to augment developed pressure during the increased afterload imposed by isometric exercise

A third small group of patients responded to isometric exercise with changes in heart rate, developed pressure and LVEDP comparable to those in Group I, however, four of these five patients failed to increase left ventricular stroke work during exercise All except one patient also failed to increase left ventricular contractility as measured by the isovolumic indices Thus it seems that this small group of patients all of whom had coronary artery disease responded to isometric exercise with a normal increase in developed pressure at the expense of less fiber shortening Thus even in the presence of an adequate pressure response, the lack of elevation of LVEDP during hand grip exercise cannot be considered normal unless flow data are available

Since isometric exercise is necessarily associated with an increase in aortic impedance a patient with mitral regurgitation might be expected to show an increase in the regurgitant fraction this is suggested by the elevation in the pulmonary capillary wedge regurgitant wave (Fig 4)

In many patients isometric exercise uncovered abnormalities of left ventricular performance that were not identified by the resting hemodynamics however the mechanism by

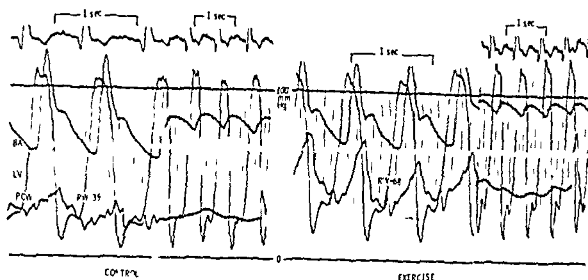


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			C	*IE*	*C*	*IE*	*C*	*IE*	*C*	*IE*	*C*	*IE*	*C*	*IE*
49/F	N	88	110	122	1 600	1 900	1 42	1 85	1 90	2 40	33	39	2 54	3 38
39/F	N	76	113	129	1 470	1 920	1 45	1 60	1 90	2 20	31	38	2 55	3 00
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Ambulatory long-term electrocardiography—the 'LCG'

Israel M Stein M D
Brookline Mass

Since the original work of Gilson Holter and Glasscock[1] in 1961 many studies have documented the diagnostic value of long term continuous monitoring of the electrocardiogram (ECG) of active subjects while they are engaged in their normal daily activities[2 7] Standard scalar electrocardiograms which are obtained in a recumbent position yield information on only 50 to 60 cardiac cycles and provide only a limited data base on which a diagnostic judgment may be made Long term continuous ambulatory monitoring of the ECG permits the examination of as many as 70 000 cardiac cycles in a 12 hour recording

This article reviews the medical indications for the use of long term ECG recordings abbreviated LCG

Instrumentation for performing the LCG

Several devices are available commercially which permit the recording on magnetic tape of the ambulatory ECG The devices vary in size weight frequency response and length of continuous recording One such device is shown in Fig 1 It consists of a one pound cassette recorder which permits up to 13 hours of continuous monitoring It may be conveniently worn beneath the clothing

The recorded tapes are reviewed at high speed using both visual scanning and computer assistance to identify abnormalities that occur during a recording period. The abnormal sequences may be printed out in standard ECG format for examination and interpretation.

Indications for monitoring

Documentation of symptoms suspected of cardiac origin LCG recordings have been proved particularly effective in detecting transient episodes of cardiac dysrhythmia and in correlating these episodes of rhythm disturbance with cardiovascular and cerebrovascular symptomatology Examples of such symptoms include palpitation chest pain dizziness syncope and shortness of breath

The symptom of palpitation which may also be expressed by a patient as the sensation of pounding racing or fluttering may be caused by various types of dysrhythmias including ectopic beats tachycardia or bradycardia Palpitations may be a manifestation of an underlying disease e g thyrotoxicosis or anemia or result from the excessive use of tobacco alcohol or such drugs as isoproterenol and aminophylline Many patients may complain of palpitations when the heart rhythm and rate are entirely normal and this symptom may only confuse a diagnosis The LCG is an effective diagnostic tool in detecting the etiology and assessing the significance of the symptom of palpitations and in permitting the institution of specific therapy

Paroxysmal atrial or ventricular arrhythmias may significantly reduce cardiac output and systemic blood pressure and may induce the symptoms of angina pectoris and the ECG signs of myocardial ischemia.[8] Impairment of cerebral blood flow may produce such neurologic symptoms as syncope convulsions hemiparesis giddiness, and dizziness.

Walter Reid and Wenger[9] evaluated 39 patients 28 with symptoms of diffuse cerebrovascu

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Repri t requests to Is ael M Stein, M D Medical Directo Cl nical D ta Serv Inc 1622 A Beacon St., Brookl n M ss 02146
Avi n s, M d l D vi on Delm Enginee ing Labs Los Angeles, Calif Cl nical D ta Services, Brookl ne Mass and Med aft, Dallas Texas.

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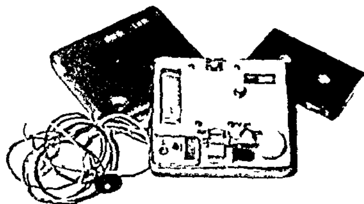


Fig 1 LCG recording unit.

lar insufficiency and 11 with transient ischemic episodes No patient had evidence of prior dysrhythmia or conduction abnormality diagnosed clinically or by a standard ECG Ten patients demonstrated significant arrhythmia on their LCG and in seven of these patients the dysrhythmia was directly correlated with symptoms Furthermore therapeutic response was demonstrated in eight patients with the initiation of specific anti arrhythmic therapy Reed Siekert and Meredith[10] recently reported that of 290 patients with cardiac dysrhythmias who received artificial pacemakers 235 manifested symptoms of generalized neurologic dysfunction and four demonstrated focal cerebral symptoms

Tamer Gellard and Garcia[11] in a brief communication reported a study in two children who developed left axis deviation and right bundle branch block after operative repair of tetralogy of Fallot These children were noted to have episodes of syncope from one to six years after surgery Standard ECG s His bundle recordings and cardiac catheterization were not helpful but the LCG revealed periods of spontaneous atrial fibrillation with rapid ventricular response in one case and episodes of bigeminy, blocked premature beats and extrasystoles in the second emphasizing the need for long term follow up after cardiac repair

Assessment of anti arrhythmic therapy

Long term ECG recordings provide one of the most practical means of evaluating the efficacy of anti arrhythmic therapy The therapeutic responsiveness to a drug, whose duration of action and peak effectiveness is defined in hours cannot be properly assessed by examining thirty to 40 cardiac cycles on a standard ECG rhythm strip

Jelinek Lohrbauer, and Lown[12] have evaluated the efficacy of quinidine and procainamide against frequent or repetitive premature ventricular beats in patients with heart disease Their study showed that only seven of seventeen patients had satisfactory response to anti arrhythmic therapy without disabling side effects They concluded that anti arrhythmic therapy requires an individual approach with knowledge of the reproducibility of the dysrhythmia in each untreated patient and that the LCG is a rational method to accomplish this purpose

The LCG is an appropriate diagnostic test at the time of institution of anti arrhythmic therapy and may be performed during the course of therapy to evaluate continued response It is also appropriate for evaluating a change in dosage and it is indicated shortly before and after discontinuation of anti arrhythmic medication to determine if cessation is tolerated without substantial worsening in frequency and type of dysrhythmia

The LCG may also be used for the assessment of the symptomatic patient with suspected malfunction of an artificial pacemaker where standard pacemaker evaluation procedures are unrevealing

Diagnosis and prognosis of coronary artery disease

The LCG has been shown to be a valuable diagnostic procedure for the assessment of patients with coronary artery disease The LCG has permitted the documentation of the etiology of such symptoms as chest pain and shortness of breath Since the standard ECG is often normal between attacks of precordial pain it is important to obtain ECG confirmation while chest symptoms are occurring The LCG has permitted the correlation of chest symptoms with objective evidence of ST segment abnormalities[13] It has not only been helpful in typical angina pectoris but has been especially useful in the Prinzmetal variant[2]

The LCG is not only valuable in diagnosis but also in assessing the prognosis of patients with coronary artery disease Kotler and co workers[14] studied the role of ventricular dysrhythmias in 160 male survivors of acute myocardial infarction using the LCG All subjects were under 65 and were functional class I or II (New York Heart Association) In the follow up period which

ranged from 30 to 54 months 14 cases of sudden cardiac death were noted. Twelve cases of sudden death (13 per cent) were observed in 87 patients with significant ventricular dysrhythmias (frequent unifocal PVC s (> 10 per hour) multifocal paired coupled premature ventricular contractions (PVC s) and ventricular tachycardia) but only two cases of sudden death were observed in 66 patients (3 per cent) with absent or infrequent premature ventricular beats (P < 0 02) These authors concluded that continuous ECG monitoring provides more accurate information on the quality and frequency of ventricular dysrhythmia information not available by standard ECG techniques.

Moss DeCamilla and Hoffman[15] studied 100 patients prospectively with continuous ECG recording just prior to hospital discharge after an acute myocardial infarction Seventeen patients died from coronary artery disease within six months after the initial recordings The characteristics which identified the high risk group were not only older age (65 ± 2 vs 57 ± 1) but increased frequency of ventricular dysrhythmias including frequent premature ventricular beats earlier PVC prematurity multifocal PVC s and pairing Two year follow up recordings in 79 survivors revealed remarkable rhythm stability between initial and follow up tracings The authors concluded that the presence of significant ventricular dysrhythmias on the LCG prospectively identified patients who are at high risk of dying in the initial six months after a myocardial infarction

Hinkle Carver and Stevens[17 18] reported a study on a random sample of 301 actively employed American men of medium age 55 years using the LCG Although totally asymptomatic of the presence of dysrhythmic cardiac function 8 8 per cent had frequent PVC s 19 1 per cent had complex ventricular arrhythmias (bigeminy trigeminy pairing and paroxysmal ventricular tachycardia) and 7 7 per cent had disturbances of intraventricular conduction Significant ventricular dysrhythmias occurred more frequently in the 58 men with definite or probable evidence of coronary heart disease and in 68 subjects who were at high risk by conventional criteria (hypertension elevated serum cholesterol and left ventricular hypertrophy on a standard ECG) The presence of significant ventricular dysrhythmia or conduction defects were associated with an enhanced risk of subsequent acute dysrhythmic death from coronary artery disease

In a recent editorial Bleifer and co workers[19] commented that routine ECG provides inadequate information on the occurrence frequency and characteristics of ventricular dysrhythmia because of the limited sample size In their study 90 per cent of the patients with paroxysmal ventricular tachycardia manifested no symptoms and the episodes were not detected by standard ECG techniques They editorialized that patients demonstrating premature ventricular contractions on routine ECG examination and those suspected of having premature ventricular contractions because of suggested symptoms should have an LCG performed during their usual activities to determine if they are at risk for paroxysmal ventricular tachycardia and by implication sudden death They additionally considered it important to study patients who are recovering from an acute myocardial infarction before discharge from the hospital since it is impossible to predict which of these patients is subject to ventricular arrhythmias on the basis of the presence or absence of these arrhythmias during the period of initial coronary care

A similar view is held by the World Health Organization Working Group on Studies of the Prodromal Symptoms in Myocardial Infarction and Sudden Death[20] They suggest that patients who have suffered a myocardial infarction should be monitored during the third week of hospitalization and that monitoring should be repeated at two months three months six months and at one year intervals

Other applications

The LCG may be used in evaluating the rehabilitative potential of the cardiac patient Norland and Semler[13] point out that the LCG is of practical value in assessing the work requirements and job capabilities of a given patient The effect of the working environment on frequency of dysrhythmia may be examined, and cardiac symptoms may be accurately assessed as they occur under normal working conditions

The LCG may be utilized to gather information on the physiologic and pathophysiologic effects of sexual intercourse in the privacy of a cardiac patient s home

The LCG is also a valuable research tool It

may be used to assess the natural history of cardiac arrhythmias,[21] for evaluating the effectiveness of experimental anti arrhythmic agents, for evaluating the efficacy of anti anginal therapy, and for determining the arrhythmogenicity of cardiac and noncardiac drugs.

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Tissue adhesive closure of aortic-pulmonary communications

James R Zuberbuhler M D
Elinor Dankner M D
Richard Zoltun R Ph
John Burkholder M D
Henry T Bahnson M D
Pittsburgh, Pa.

Aortic pulmonary artery communications can take several forms including patent ductus arteriosus aortic pulmonary window truncus arteriosus and precapillary anastomosis of a bronchial or coronary artery to a pulmonary artery In the presence of marked pulmonic stenosis or of pulmonary atresia such pathways may be an indispensable source of pulmonary blood flow but in the absence of severe right ventricular outflow obstruction these connections are deleterious Although repair is relatively easy if the communication is a simple patent ductus arteriosus surgical correction is difficult and carries a considerable risk when large bronchial collateral vessels accompany tetralogy of Fallot or transposition of the great arteries[1,2] In such cases nonoperative occlusion of an aortic pulmonary communication might be an alternative to surgery The following report describes an experimental model for testing the feasibility of occluding an aortic pulmonary artery connection with tissue adhesive and presents a case report of a patient successfully treated by this technique

Materials and methods

Experimental model In each of eight mongrel dogs a segment of subclavian artery was excised and anastomosed end to side with the aorta and left pulmonary artery simulating a patent ductus arteriosus One month later cardiac catheterization was performed and patency of the aortic pulmonary artery connection was confirmed by catheter pass and cineaortography A previously prepared adhesive delivery system (Fig 1) was introduced into the right femoral artery and positioned in the aortic pulmonary fistula In four dogs (Group I) the aortic end of the fistula was temporarily occluded with a balloon catheter and in the other four dogs (Group II) the pulmo

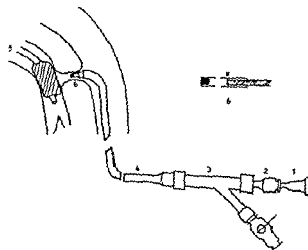


Fig 1 Schematic representation of the adhesive delivery system positioned in the aortic end of the aortic pulmonary fistula and of the balloon catheter in the left pulmonary artery (1) Formocath adhesive delivery catheter (2) Formocath conduit catheter (0 037 by 0 048 inch) (3) Side arm adapter (4) No 7 French Lehman catheter (5) No 8 5 French Dotter Lukas catheter (6) Inset (a) 0 010 by 0 020 inch Formocath (b) 0 012 by 0 025 inch Silastic tubing with two side holes and (c) stainless steel tip

From the Children's Hospital of Pittsburgh and the Department of Pediatrics and Surgery of the University of Pittsburgh Pittsburgh Pa.

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Reprint requests to James R. Zuberbuhler M D Children's Hospital of Pittsburgh 125 De Soto St. Pittsburgh, Pa 15213

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Experimental and laboratory reports

Tissue adhesive closure of aortic-pulmonary communications

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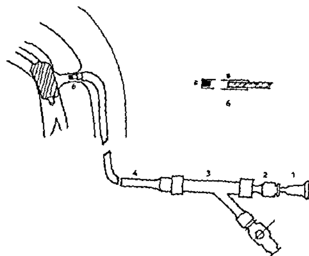


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F om the Children s Hosp tal of P ttsb rgh nd the Departments of Pediatrics nd Surg ry of the Un v rsity f P ttsburgh Pitt burgh Pa.

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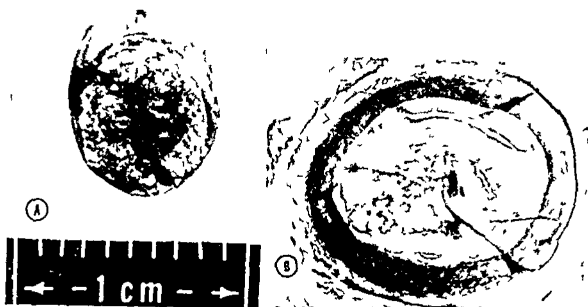


Fig 2 A and B Cross section of an occluded aortic pulmonary fistula *A Gross section. B Microscopic* the clear areas in the lower portion represent polymer matrix not yet invaded by fibrous tissue There is a sectioning artifact in the upper portion



Fig 3 Main pulmonary artery selective cineangiogram showing *hypoplastic pulmonary arteries*

nary end of communication was so occluded. Successful blocking of the aortic pulmonary fistula was signaled by disappearance of the murmur heard through an esophageal stethoscope and was confirmed by injection of contrast medium into the side arm of the adhesive delivery system Contrast medium was flushed from the aortic pulmonary fistula with 5 per cent glucose and water and the Formocath tubing was advanced so that the metal tip was in the midportion of the fistula The tubing was flushed with 5 per cent glucose and water and from 0 1 to 0 3 ml of Bucrylate (isobutyl 2 cyanoacrylate) (Ethicon Inc , Summerville N J) was slowly delivered into the fistula After one minute, the balloon was deflated and the adhesive delivery system was withdrawn Aortic and pulmonary cineangiograms were repeated to assess completeness of occlusion and to identify encroachment on the lumen of the aorta or pulmonary artery In two dogs Bucrylate injection was repeated because of incomplete occlusion following the initial injection

One to six months later catheterization and angiographic studies were repeated and seven of the eight animals were sacrificed In each of the seven animals the aorta and pulmonary artery were inspected and a search was made for gross and microscopic pulmonary and systemic emboli

Results Studies with contrast medium immediately after Bucrylate injection showed complete occlusion in three dogs and nearly complete occlusion in the other five dogs Cineaortography one to six months later demonstrated complete occlusion in all dogs No aortic filling defects were identified in any dog and left pulmonary artery filling defects were seen in Group I dogs only

Postmortem examination confirmed the cineangiographic findings The fistula was com



Fig 4 A and B A, Left bronchial artery before occlusion and *B* after occlusion

pletely occluded in all dogs (Fig 2 *A*) Sections through the aortic pulmonary fistula showed infiltration of inflammatory cells and fibrous tissue into the Bucrylate mass (Fig 2 *B*) Free surfaces of the mass was endothelialized No systemic embolization of tissue adhesive could be demonstrated grossly or microscopically All animals in Group I had microscopic pulmonary embolization of Bucrylate One Group II dog showed microscopic emboli in the upper lobe of the right lung and one small embolus in the lower lobe of the left lung No animal had clinical illness during the period of observation and none had pulmonary hypertension at repeat catheterization

Case report

At age 5 years E C was first admitted to this hospital with status asthmaticus thought to be secondary to infestation with visceral larva migrans He was successfully treated with thiabendazole but was readmitted two months later in congestive heart failure His weight was 15 kilograms and his height was 101 centimeters, both at the third percentile There was a Grade III/VI systolic ejection murmur at the mid left sternal border and a Grade III/VI continuous murmur at the base and over the posterior thorax The liver edge was palpable 6 cm below the right costal margin and the spleen tip was felt at the left costal margin S_2 was single No ejection click or gallop was present. There was 1+ cyanosis of the lips and nail beds An electrocardiogram disclosed biatrial enlargement and biventricular hypertrophy Chest x ray showed marked cardiomegaly a large aorta and increased pulmonary vascular markings He improved with digitalization

Cardiac catheterization was done and the hemodynamic findings are summarized in Table I Selective cineangiograms showed a ventricular septal defect valvular and infundibular pulmonic stenosis hypoplastic pulmonary arteries (Fig 3) and two large bronchial arteries (Figs 4 *A* and 5 *A*) which arose from the descending aorta These collateral vessels anastomosed to the right and left pulmonary arteries and appeared to supply much of the pulmonary blood flow

Surgical repair was advised and informed consent to the use of the tissue adhesive Bucrylate was obtained from the parents On the day of surgery the patient was brought to the catheterization laboratory and an NIH catheter was placed in the aorta A No 5 Swan Ganz catheter modified by adding a Formocath extension and a tear away tip of 20 gauge Silastic tubing with four side holes and a metal plug in the tip was sprayed with Antifoam A (Dow Corning) and was inserted percutaneously into the left femoral artery The balloon was positioned in the left bronchial artery and was inflated Aortography showed complete occlusion of the bronchial ves

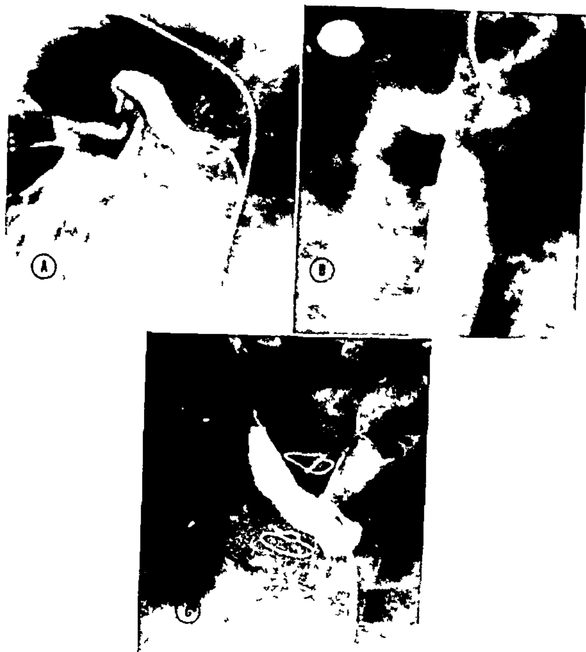


Fig 5 A B and C A Right bronchial before occlusion B, with adhesive delivery system in place and C, after occlusion

sel Bucrylate 0 2 ml, was delivered into the bronchial artery distal to the balloon The balloon was deflated and removed. Nearly complete occlusion of the vessel was demonstrated by aortogram A similarly prepared catheter was placed in the right bronchial artery (Fig 5 B) and the patient was taken to the operating room Following institution of cardiopulmonary bypass the balloon was inflated and 0 5 ml of Bucrylate was delivered The ventricular septal defect was patched, the infundibular pulmonic stenosis resected and the pulmonic valve largely removed

During the postoperative period the patient continued to show signs of right heart failure and to have a loud continuous murmur A Grade III medium pitched diastolic murmur was heard along the left sternal border and was thought to represent pulmonic insufficiency Repeat catheterization one month later demonstrated the presence of a large previously unsuspected bronchial artery (Fig 6 A) which arose from the aortic arch and supplied branches to both right and left pulmonary arteries An oxygen step up was present in the distal right pulmonary artery and a pulmonary to systemic flow ratio of 2 1 was calculated This bronchial artery was occluded with Bucrylate Selective injection of contrast media into the proximal portion of the three

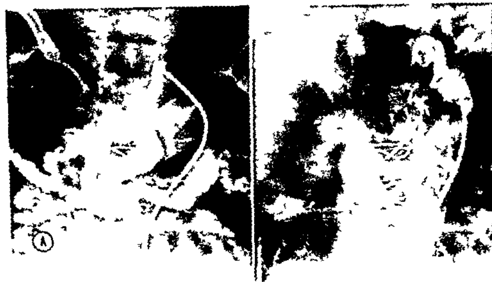


Fig 6 A and B A Large bronchial artery arising from the arch of the aorta and supplying both lungs B after occlusion.

Table I Catheterization data

Site	Preoperative		Postoperative	
	Per cent saturation	Pressure (mm. Hg)	Per cent saturation	Pressure (mm. Hg)
SVC	56	–	74	–
RA	57	(5)	73	–
RV	62	95/0 ED 9 12	75	85/0 ED 10
MPA	82	(30)	76	60/10(25)
RPA	–	–	84	32/10(18)
LA	–	–	–	(5)
LV	86	95/0 ED 11	–	90/0 ED 8
AO	84	95/65(82)	100	90/65(75)
Cardiac index	2 8 L/min/M^2		1 9 L/min/M^2	

( ) = Mean pressu

bronchial arteries demonstrated complete occlusion of two and nearly complete occlusion of the third (Figs 4 B 5 C and 6 B) Following this procedure congestive heart failure abated and the continuous murmur disappeared A soft systolic murmur persisted at the mid high-left sternal border and the murmur of pulmonic insufficiency became much softer The patient is currently doing well five months after operation

Discussion

The tissue adhesive Bucrylate has a low viscosity and polymerizes rapidly on contact with blood, forming a hard spongy matrix The blood trapped in the interstices is replaced by fibrous tissue The histotoxicity seems to be low an earlier experimental study showed only shrinking and hyperchromatism of a few nuclei in the media of arteries occluded by Bucrylate [3]

Bucrylate has been used in the treatment of cerebrospinal fluid rhinorrhea [4] lacerations of the liver [5] and to occlude intracranial aneurysms and arterio venous malformations [6,7] Its application to congenital heart disease has not been previously explored.

Zanetti and Sherman showed that temporary stasis was necessary if distal embolization was to be avoided.[3] Since the aortic pulmonary com

munication in our experimental model was too short to permit occlusion of the fistula by means of a balloon placed in the communication itself, we attempted to achieve stasis either by temporarily obstructing the aorta at the proximal end of the fistula or by occluding the left pulmonary artery at the distal end Bucrylate injection resulted in complete occlusion in every case Pulmonary embolization and partial occlusion of the left pulmonary artery occurred only in Group I dogs In our patient, temporary occlusion was easily accomplished since the balloon could be positioned in the bronchial artery itself This precluded systemic embolization and significant embolization to the true pulmonary arteries seemed unlikely

In our patient it was possible to demonstrate large percapillary anastomoses with the pulmonary arterial tree It seemed advisable to occlude the major bronchial arteries before attempting intracardiac repair in order to reduce the large pulmonary venous return that would have made operative repair difficult. Closure with tissue adhesive seemed preferable to surgical exposure and ligation of the thin and tortuous bronchial arteries through the usual median sternotomy A case similar to ours was reported by Lintermans, Guntheroth, and Figley[2] and surgical intervention was deferred because of the anticipated high risk

In our case it was felt that occlusion of all bronchial arteries prior to the institution of cardiopulmonary bypass would probably result in death since the major portion of pulmonary blood flow appeared to be by way of these collateral vessels Permanent occlusion of one vessel and placement of a balloon catheter in another vessel prior to transfer to the operating room proved to be safe and effective Our failure to demonstrate and occlude a third large bronchial artery prior to surgery probably contributed to congestive heart failure in the early postoperative period

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The treatment of angina pectoris with alpha methyldopa

Rand T Frederiksen M D *
Melvin D Cheitlin M D F A C C
D Roy Ferguson M D
With the technical assistance of Judy Fortier
Aberdeen, Md.

Antihypertensive agents have been shown to reduce the frequency and severity of angina pectoris in patients who have both hypertension and coronary artery disease [1,2] In addition it has been well established that hypertensive patients with angina increase their exercise tolerance when blood pressure is reduced during exercise [3] For these reasons it is of considerable interest to determine the precise effect of an antihypertensive agent on blood pressure during exercise and to determine the effect of the antihypertensive agent on non hypertensive patients with angina A double blind crossover study was done using alpha methyldopa in six normotensive patients with stable angina pectoris in order to elucidate those effects

Methods

Subjects Six patients five men and one woman aged 41 to 66 years (mean 46 years) with a clinical history of typical stable angina pectoris were included in the study All of the six had a positive electrocardiographic response to exercise and no patient had valvular heart disease congestive heart failure or cardiomegaly Three had suffered well documented myocardial infarctions None of the patients had a history of hypertension and all had a standing diastolic blood pressure less than 90 mm Hg (average standing B.P = 123/81) Except for nitroglycerine the only drugs taken by the patients were procainamide in one instance (Patient 2) and isosorbide dinitrate (not taken the days of exercise testing) in Patient 3

Exercise The exercise tests were performed in the afternoon with all patients omitting lunch on the day of the test Each patient performed a standard multi stage exercise test on a motorized treadmill (Collins Executread, P 2050) After each patient was familiarized with the equipment and procedure he began walking at 2 2 mi /hr for three minutes at zero grade This was followed by three minute walks at 3 per cent grade 6 per cent grade and 9 per cent grade in a stepwise fashion Arterial pressure was measured by auscultation immediately prior to the end of each stage of exercise heart rate was determined from a continuous electrocardiographic recording visible to the physician during exercise All exercise tests were done in duplicate the second test was begun when the heart rate had returned to the original level. The duplication of tests showed an average reproducibility of ± 18 seconds with a range from ± 0 to ± 57 seconds The possible significance of the difference of exercise performance times while on alpha methyldopa as opposed to placebo was tested by means of the paired t test and the null hypothesis

Electrocardiograms The exercise electrocardiogram was recorded from a bipolar V_5 lead system with the left chest lead at V_5 and the right chest lead at the right shoulder A continuous electrocardiographic record was made during each exercise test Exercise was terminated for

From the Department of Med cine U S Kirk Army Hospital, Aberdeen Proving Ground, Md. nd Divis n of Card ology Walter Reed Gene l Hosp tal, Washington, D C

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R p int requests to: Dr Rand T Frederiksen, Roy l Postgraduate M dical School, Division of Cardiology Hammersmith Hospital, London W12 OHS United K ngd m.

* Current ddress Royal Postgraduate Medic l School, Divis n of Ca diology H mmersmith Hospital, London.

Table I Exercise performance before and during antihypertensive therapy

Patient		*Exercise duration (sec.)*	*Mean maximum heart rate (beats/min.)*	*Mean peak systolic B P * (mm. Hg)*	*Mean rate × pressure product (10^4)*
1	Control	185 ± 32	132 ± 4	159 ± 1	2 1 ± 04
	Treatment	217 ± 8	131 ± 1	155 ± 5	2 0 ± 05
2	Control	302 ± 40	146 ± 5	145 ± 14	2 1 ± 25
	Treatment	299 ± 4	150 ± 0	120 ± 5	1 8 ± 15
3	Control	247 ± 76	111 ± 10	166 ± 13	1 9 ± 30
	Treatment	334 ± 2	115 ± 0	170 ± 20	1 9 ± 22
4	Control	148 ± 51	131 ± 4	185 ± 5	2 4 ± 09
	Treatment	336 ± 12	135 ± 2	180 ± 0	2 4 ± 04
5	Control	284 ± 38	137 ± 4	140 ± 0	1 9 ± 06
	Treatment	459 ± 21	138 ± 0	135 ± 5	1 8 ± 07
6	Control	433 ± 143	146 ± 8	183 ± 7	2 7 ± 21
	Treatment	513 ± 1	152 ± 2	150 ± 0	2 3 ± 03

B P = blood pressure ST↓ = ST segment depression mpr = maximum predicted heart rate
†Probability that exercise duration difference is due to chance

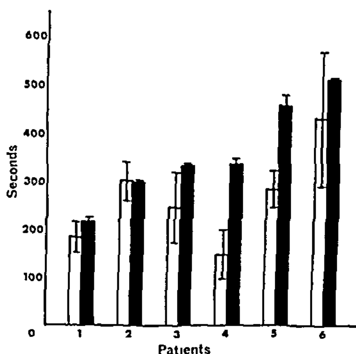


Fig 1 Exercise duration before and after antihypertensive therapy Duration of exercise in seconds (*vertical axis*) in dividual patients on the *horizontal axis* Clear bars indicate exercise duration during therapy Error bars show standard deviation

(1) chest pain, (2) ST depression of 1 0 mm with a flat or downsloping segment, (3) a heart rate of 85 per cent of the predicted maximum or (4) severe dyspnea or fatigue

Plan of study The study was designed as a double blind crossover with each patient serving as his own control Each patient had an exercise test and was then randomly assigned to either a placebo or treatment group The patients were started on one placebo capsule twice a day or 250 mg of alpha methyldopa twice a day The num ber of capsules was increased two at a time at three to six day intervals until a maximum of eight capsules per day were taken, or until the standing diastolic blood pressure after two minutes was 10 mm Hg lower than the control observations Alpha methyldopa or placebo was then continued for seven days and the patients were again exercised After the second exercise test all patients were placed on placebo for seven days and a third exercise test was done The pa tients who were originally taking placebo were then placed on alpha methyldopa and the pa tients taking alpha methyldopa were started on placebo The dose was again titrated for each pa tient, the maximum dose continued for seven days and the fourth exercise test was done In order to protect the double blind aspect of the study, the exercise tests were done by a physician who had not been adjusting the drug dosages (D R F and R T F) Informed consent was ob tained from each patient prior to entrance into the study No adverse effects were observed dur ing the program which required the withdrawal of any patient from the protocol

Results

Heart rate and blood pressure Table I sum marizes the results of the 48 exercise tests and the resting blood pressure determinations Four

End points	*No of tests*	*Resting B.P* *	*Alpha methyldopa (Gm.)*	*P*†
pain	6	113/77	0 0	
pain	2	110/80	2 0	0 6
ST↓ and mpr	6	118/87	0 0	
mpr	2	98/78	1 5	0 9
ST↓ and pain	6	138/87	0 0	
ST↓	2	130/80	1 0	0 6
dyspnea	6	143/87	0 0	
dyspnea	2	130/80	0 5	0 1
mpr	6	110/69	0 0	
mpr	2	108/60	1 0	0 1
pain and mpr	6	124/84	0 0	
mpr	2	130/90	2 0	0 7

of the six patients had an average decrease of 8 mm. Hg in standing blood pressure while two patients had no significant change in resting blood pressure while on two grams of alpha methyldopa per day There was no significant difference in maximum heart rate or blood pressure during exercise while the patients were on either placebo or alpha methyldopa Likewise the rate pressure products at the exercise end point were not statistically different in any patient whether on alpha methyldopa or not

Duration of exercise Fig 1 and Table I demonstrate the change in exercise duration on alpha methyldopa as compared to placebo The results of all six exercise tests done prior to any therapy and on placebo are shown together as the control. The treatment values represent the exercise tests done in duplicate while on alpha methyldopa Although there was a trend toward an increase in exercise duration while on the drug the differences were not significant using the paired t test as the criterion for significance In no case however did exercise performance deteriorate while on alpha methyldopa

Discussion

The results of this study demonstrate that ambulatory patients with normal blood pressure and stable angina pectoris who are not in congestive heart failure have no change in peak systolic blood pressure heart rate or exercise performance when placed on antihypertensive therapy Earlier studies of exercise performance in patients with hypertension complicated by hypertensive heart disease have shown an improvement in exercise performance and a decrease in peak systolic blood pressure when the resting pressure was lowered [1,4,5] Bruce and colleagues[5] found that patients with hypertension which was not complicated by clinical manifestations of disease had no change in peak systolic pressure or exercise performance when placed on chronic antihypertensive therapy The improvement in his patients with hypertensive heart disease was felt to be due to correction of the noncongestive left ventricular failure which occurred at higher work loads The results of this present study suggest that normotensive patients with angina behave much like those with uncomplicated hypertension and do not develop symptomatic left ventricular failure most likely because exercise was terminated by chest pain before left ventricular dysfunction became prominent Exercise performance did not deteriorate in any of the patients and no one was withdrawn from the study due to an increase in angina

It can be concluded from the findings of this study and from the previous work of Bruce and colleagues[5] that patients with angina pectoris uncomplicated by congestive heart failure exhibit no change in exercise performance when treated with an antihypertensive agent Termination of exercise by chest pain before symptomatic left ventricular failure could develop possibly precludes benefit from the antihypertensive agent Since the only observed effect of the administration of alpha methyldopa on these patients was to lower the resting blood pressure the consistency and stability of exercise performance must be due to the fact that the exercising blood pressure in unchanged by antihypertensive agents in patients with angina pectoris

Summary

In order to determine whether exercise performance could be improved by using alpha methyldopa to lower the resting diastolic blood pressure a double blind crossover study was carried out in six normotensive patients with angina pectoris Duration of exercise peak systolic blood pressure and maximum heart rate were all unchanged during treatment It is suggested that patients with angina pectoris behave much like patients with uncomplicated hypertension who

do not improve their exercise performance when treated with an antihypertensive agent

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Systemic and coronary hemodynamic effects of intracoronary administration of prostaglandins E_1 and E_2

George G Rowe M D
Skoda Afonso M D Ph D
Madison, Wisc

The circulatory effects of prostaglandins (PG) have been extensively investigated and recently summarized.[1] Detailed studies of the effects of PGA_1 on the systemic and coronary circulation of conscious dogs have been reported,[2] as have studies of the effects of PGA_1 on several vascular beds in man[3] A recent review hypothesizes that prostaglandins are important intrarenal hypotensive vasoregulatory compounds which favorably moderate the vascular response to vasoconstrictors[4] In support of this it has been postulated that prostaglandins act as modulators of the adrenergic neuro transmission to blood vessels[5] Obviously it is important to know the coronary vascular response to such compounds

It has been reported that PGE_1 and PGA_1 produce coronary vasodilatation on direct intracoronary arterial infusion into the open chest dog[6,8] whether the heart was beating fibrillating or arrested.[6] The coronary vasodilatation was not accompanied by an increase in the arteriovenous oxygen difference or in myocardial oxygen consumption[6] It has also been reported in the open chest right heart bypass dog that coronary blood flow decreases parallel to the decrease in blood pressure when PGA_1 is given[9] and that PGE_1 and PGE_2 inhibit the coronary vasodilatation metabolically induced by norepinephrine and $CaCl_2$[10] and diazoxide[11] Since results of these studies appear divergent and since the latter studies were done in open chest anesthetized dogs which had had considerable surgery the present study was done to determine the effects of PGE_1 and PGE_2 in intact anesthetized mongrel dogs In view of the proposed relation of prostaglandin compounds to neuro transmission[5] studies were also done before and subsequent to beta adrenergic blockade utilizing propranolol and sotalol Both of these beta adrenergic blockers were used because the response to glucagon differs greatly in dogs pretreated with propranolol as compared to those given sotalol.[12] To avoid a marked systemic effect which in some studies seems to have obscured local coronary effects[9] the compounds were given directly into the left coronary artery

Materials and methods

For this study 44 mongrel dogs were anesthetized with 3 mg per kilogram of body weight of morphine sulphate subcutaneously followed one half hour later by 0 25 mg per kilogram of body weight of a 50/50 mixture of Dial urethane* and pentobarbital This anesthetic gives a prolonged stable state with a heart rate around 100 beats per minute and with sinus arrhythmia similar to that of a resting dog It has been shown by long experience in this laboratory to give a suitable state for pharmacologic studies where results of hemodynamic studies closely reproduce those obtained in unanesthetized man After anesthesia was induced three Cournand needles were inserted percutaneously into the femoral arteries These were used for recording pressure aspirat

From the Cardiovascular Research Laboratory Department of Medicine University of Wisconsin Medical School, Madison, Wisc

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Reprint request to Dr George G Rowe Cardiovascular Research Laboratory Department of Medicine University of Wisconsin Medical School, 1300 University Ave Madison, Wisc 53 06

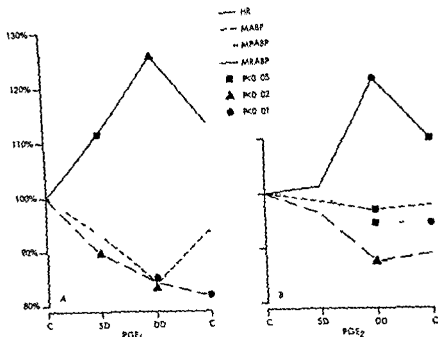
*Dial urethane contains dial (diallybarbituric acid) 100 mg /ml. monoethylurea 400 mg /ml and urethane 400 mg /ml Veterinary pentobarbital contains 60 mg /ml of pentobarbital.

ing blood for indicator dilution curves and sampling for blood oxygen content Through the external jugular vein two catheters were manipulated flouroscopically into the pulmonary artery One was used for pressure recording and blood sampling and the other for injecting indocyanine green for indicator dilution curves Two catheters were introduced into the coronary sinus One of these was a thermodilution flowmeter for measuring coronary sinus blood flow[13] and the other was a number six catheter for sampling of blood for oxygen content Long experience in this laboratory shows these two catheters do not produce any evidence of significant obstruction to coronary sinus blood flow or alteration of expected coronary hemodynamic responses A catheter was inserted into the right atrium for pressure measurement and a catheter with a basket tip to prevent wedging and obstructing the coronary arteries was introduced through the carotid artery into the left coronary artery and positioned in the proximal part of the left anterior descending coronary artery A Gilson dye tracer recording on a Gilson macropolygraph inscribed indicator dilution curves used for determining cardiac output, and Statham p23Db strain gauge pressure transducers were used for pressure recording Mean pressure was determined by electrical damping Standard calculations were used for cardiac output and work and the t test for paired values was used for statistical analysis

When the dogs were studied PGE_1 or PGE_2 was infused through the intracoronary arterial catheter with a Harvard Apparatus Company constant infusion device By trial a dose of PGE_1 was established in each of 11 dogs which would produce a reasonable increase in coronary blood flow The infusion was discontinued and the dog was observed until its effects dissipated Control observations of systemic and coronary hemodynamics consisting of cardiac output coronary flow, heart rate, and pressures in the femoral and pulmonary arteries and the right atrium were then made and repeated during a steady infusion of the previously determined dose of PGE_1 (average 8 7 mcg per minute), as well as during infusion of approximately twice this dose (21 4 mcg per minute) The infusion was then discontinued and the coronary flow responses monitored until it had returned to the baseline, then control observations were repeated Blood specimens were drawn from the coronary sinus pulmonary artery, and femoral artery in the control state during the peak of the response to each dose of PGE_1 and again as a final control when the effects of the compounds on coronary flow had dissipated Blood samples were analyzed in duplicate with the Lexicon Blood Gas Analyzer to determine oxygen content The same procedure was then repeated in 11 dogs with PGE_2 utilizing a smaller (5 5 mcg per minute) and a larger (10 9 mcg per minute) rate of infusion

In six dogs the coronary vasodilator response to intracoronary administration of PGE_1 and PGE_2 was compared To do this coronary sinus flow was monitored continuously and the response for example, to infusion of 10 mcg per minute infusion of PGE_1 was determined The infusion was discontinued and coronary flow observed continuously until it had returned to control, then an infusion of 10 mcg per minute of PGE_2 was given and the observations were repeated The same set of observations were made studying either 5 10, or 20 mcg of PGE_1 and PGE_2 In some instances when a plateau of effect was reached to PGE_1 a stopcock was switched and an equal dose of PGE_2 was substituted without any break in the infusions The response was then compared The experiment was repeated nine times in six dogs.

The next part of the study consisted of determining the response to PGE_2 during beta adrenergic blockade In four dogs PGE_2 was infused into the coronary artery at 5 and 10 mcg per minute subsequent to induction of beta blockade In two of these dogs the blockade was induced by 1 mg per kilogram of body weight of propranolol and in two by 2 5 mg per kilogram of body weight of sotalol PGE_2 was then administered at an average rate of 2 3 mcg per minute into the coronary artery in a group of 11 dogs before and after they were given 1 mg per kilogram of body weight of propranolol The rate is given as an average because in each dog a suitable rate of infusion was selected to produce a good response in the coronary sinus blood flow prior to beta blockade When this dose was established the infusion was discontinued and coronary flow and other parameters were permitted to return to the baseline Control systemic and coronary hemodynamic effects were made and then the effects of a known single effective dose of PGE_2 were determined as already described



F g 1 These graphs depict the changes which occurred when PGE_1 and PGE_2 were infused into the left coronary artery of an intact anesthetized dog For each parameter in this and succeeding graphs the control value is taken as 100 per cent and any deviation plotted in per cent change from this number The four data points along the baseline are obtained during the control state during intracoronary infusion of the first dose of prostaglandin during infusion of approximately twice the first dose of prostaglandin, and after the infusion had been discontinued The time at which the final data point was taken was determined by continuous observation of the rate of coronary blood flow and data was collected when the control value was reached. The statistical significance of data points as estimated by the *t* test and the parameter de picted are indicated by the key in the center between the two graphs *HR* = heart rate *MABP* = systemic arterial mean blood pressure *MPABP* = pulmonary arterial mean blood pressure *MRABP* = mean blood pressure in the right atrium

above Then beta blockade was induced with 1 mg per kilogram of body weight of propranolol intravenously As soon as the hemodynamic state was stable control and experimental observations were repeated infusing the same average dose of PGE_2 In a second group of seven dogs similar observations were made with intracoronary admistration of an average of 6 mcg per minute of PGE_2 before and after they were given 2 5 mg per kilogram of body weight of sotalol to induce beta blockade The studies were done in the same manner as has already been described except that sotalol was substituted for propranolol to induce beta adrenergic receptor blockade Each dog served as his own control and observations were made of the same parameters as in the initial study

In Tables I and II and in the graphs are shown the hemodynamic response in intact anesthetized mongrel dogs to the intracoronary administration of PGE_1 and PGE_2 In each case the original control observation is taken as 100 per cent and the change is plotted in per cent for each parameter from that figure The data points for each parameter were collected as closely to simultaneous as was practicable Determinations were made when a stable coronary flow was recorded at each level of prostaglandin infusion and again when the coronary flow had returned to the control level It is clear from the graphs that not all parameters returned to the baseline simultaneously but the effects of prostaglandin had largely subsided when the final measurement was made

To determine whether PGE_1 and PGE_2 were more or less effective per unit weight than the known active coronary vasodilator adenosine these three compounds were infused consecutively into the same coronary artery of the same dog Coronary sinus blood flow was monitored continuously with the thermodilution flowmeter A series of infusion rates of each sub

ing blood for indicator dilution curves and sampling for blood oxygen content Through the external jugular vein two catheters were manipulated flouroscopically into the pulmonary artery One was used for pressure recording and blood sampling and the other for injecting indocyanine green for indicator dilution curves Two catheters were introduced into the coronary sinus One of these was a thermodilution flowmeter for measuring coronary sinus blood flow[13] and the other was a number six catheter for sampling of blood for oxygen content Long experience in this laboratory shows these two catheters do not produce any evidence of significant obstruction to coronary sinus blood flow or alteration of expected coronary hemodynamic responses A catheter was inserted into the right atrium for pressure measurement and a catheter with a basket tip to prevent wedging and obstructing the coronary arteries was introduced through the carotid artery into the left coronary artery and positioned in the proximal part of the left anterior descending coronary artery A Gilson dye tracer recording on a Gilson macropolygraph inscribed indicator dilution curves used for determining cardiac output and Statham p23Db strain gauge pressure transducers were used for pressure recording Mean pressure was determined by electrical damping Standard calculations were used for cardiac output and work and the t test for paired values was used for statistical analysis

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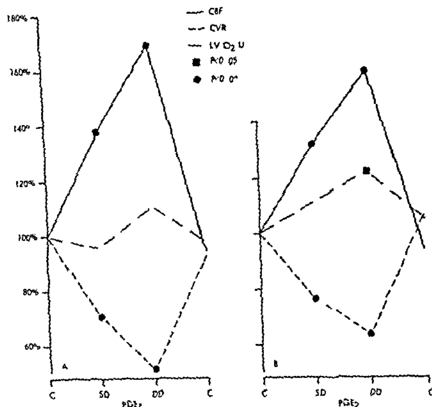


Fig 4 See legend for Fig 1 *CBF* = coronary sinus blood flow *CVR* = calculated coronary vascular resistance measured as MABP ÷ flow *LVO_2U* = left ventricular oxygen consumption.

3*B* there was a trend for both peripheral and pulmonary resistances to be reduced during the infusion of prostaglandin with the decrease in total peripheral resistance reaching significance during infusion of PGE_1 whereas the decrease in total pulmonary resistance was significant during infusion of PGE_2 The fact that these returned quickly toward the control value when the infusion was discontinued supports the idea that the changes were produced by PGE_1 and PGE_2.

As was expected from the point of infusion and as shown in Figs. 4*A* and 4*B* the major changes were seen in the coronary circulation Both PGE_1 and PGE_2 produced a significant dose related reduction in coronary vascular resistance accompanied by a marked increase in coronary blood flow Cardiac oxygen consumption increased slightly during the higher dose of PGE_1 but this change was not statistically significant. During administration of the larger dose of PGE_2 the 20 per cent increase in left ventricular oxygen consumption did reach statistical significance The change in left ventricular oxygen consumption was small however compared to the increase in coronary sinus oxygen content.

During beta adrenergic blockade with propranolol or sotalol as tested in each of two dogs the intracoronary administration of increasing doses of PGE_2 produced progressive coronary vasodilatation with a rise in coronary sinus oxygen content and a decrease in coronary vascular resistance This did not answer the question as to whether the response was quantitatively diminished, however, and this information was sought in the further systematic study of larger groups

As seen in Table III the administration of propranolol decreased the response of the heart rate to infusion of PGE_2 into the coronary artery The systemic arterial blood pressure fell a comparable amount with PGE_2 before and after propranolol but there were no significant changes in the pressure in the pulmonary artery or the right atrium Prior to administration of propranolol coronary blood flow increased 26 per

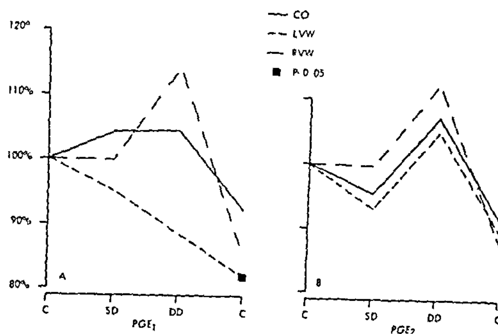


Fig 2. See legend for Fig 1 *CO* = cardiac output *LVW* = left ventricular work *RVW* = right ventricular work.

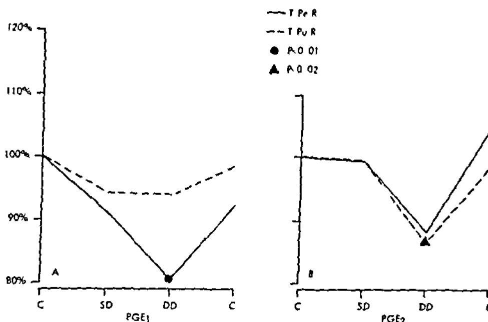


Fig 3 See legend for Fig 1 TPeR = total peripheral resistance *TPuR* = total pulmonary resistance

stance were given to each dog and the coronary flow response was determined. Equally active doses were established as judged by the flow achieved during continuous intracoronary arterial infusion In each determination the effect of one compound was permitted to dissipate before a second compound was tested

Results

The results are displayed in both tables and the graphs (Figs 1 through 4) Table I presents the numerical data on PGE_1 and Table II shows that on PGE_2 It can be seen in Fig 1*A* that administration of PGE_1 into the left coronary artery was associated with a progressive and significant increase in heart rate and decrease in pressure in the systemic arteries and in the right atrium Pulmonary arterial pressure changes were minor and insignificant. Fig 1*B* shows that intracoronary arterial PGE_2 on the other hand was associated with a similar rate change but a small consistent, and statistically significant reduction in pressure in the systemic and pulmonary arteries and the right atrium There were minor fluctuations in cardiac output, and left ventricular work as seen in Figs 2*A* and 2*B* but no significant changes occurred during the infusion of PGE_1 or PGE_2 in these animals As seen in Figs 3*A* and

Table II Systemic and coronary hemodynamic effects of a single and double dose of intracoronary PGE_2

Parameter	*Control*	*PGE_2 (5 5 mcg /min.)*	*PGE_2 (10 9 mcg /min.)*
Heart rate (beats/minute)	94	95	113†
Mean arterial blood pressure (mm Hg)	121	119	117
Mean pulmonary arterial blood pressure (mm. Hg)	17	17	16
Mean right atrial blood pressure (mm Hg)	5 5	5 3	4 6†
Arterial oxygen content (ml /100 ml blood)	17 0	17.2	17 5
Arterial mixed venous oxygen difference (ml /100 ml blood)	4 1	3 7	3 5
Coronary sinus oxygen content (ml./100 ml. blood)	6 8	8 7‡	9 2‡
Cardiac output (L /minute)	3 49	3 33	3 76
Stroke volume (ml)	37	36	34‡
Left ventricular work (Kg M /minute)	5 8	5 4	6 1
Right ventricular work (Kg M /minute)	0 8	0 8	0 9
Total peripheral resistance (c g s units)	2 958	2 950	2 610
Total pulmonary resistance (c g s units)	417	418	360†
Coronary sinus blood flow (ml /minute)	44	58‡	69‡
Coronary vascular resistance (units)	2 94	2 24‡	1 88‡
Left ventricular oxygen usage (ml /minute)	4 6	5 2	5 6

P < 0 05
†P < 0 0
‡P < 0 01

tance[14] Pulmonary vasodilatation by PGE_1 and constriction of $PGF_{2\alpha}$ has been reported by others[15] By the present experimental design small doses of PGE compounds were given directly into the coronary artery hence only a low concentration reached the pulmonary vessels and little change occurred in pulmonary hemodynamics

Previous studies indicate widespread vasodilatation in regional circulations by PGE_1 E_2 A_1 and $F_{2\alpha}$ in the dog hindpaw[5] by PGE_1 and PGF_2 in the peripheral arteries of the cat[16] by PGA_1 A_2 B E_2, and $F_{2\alpha}$ on the forearm arteries of man[17] and in visceral arteries of many species as summarized by Nakano and colleagues[1 6]

The results concerning cardiac output are scattered, with some indicating an increase in open chest dogs with PGE_1 PGA_1 and PGF_2[18] an early increase in output with PGE_1 and PGA_2 which is followed by reduction[6] no change following PGE_1 PGE_2, and PGA_1[19] no change with PGE_2 and PGF_2 in cattle[20] and no change when PGF_2 is given to pregnant women[21] This variability of response may well be related to whether the relaxation of peripheral veins exceeds that in peripheral arteries PGE_2 and PGA_2 can dilate veins in man[22] If venous relaxation is the greater cardiac filling pressure would be expected to decrease and cardiac output to fall, whereas if the arterial pressure fell more and venous pressure were maintained cardiac output should rise because cardiac contractility tends to increase[8,22 24] On the other hand, PGB_1 and PGF_2 cause constriction of the circular muscle of human superficial veins[22] and such action might support venous return and increase cardiac output. No significant change occurred in cardiac output in the present study probably because a small dose of prostaglandin was given directly into the coronary arteries

Considerable increase in cardiac rate occurred with PGE_1 and PGE_2 in the present study until after propranolol and sotalol, when there was little change The rate change is generally thought to be reflex in origin since it does not occur after combined beta receptor and cholinergic nerve fiber blockade in the conscious dog[2] and PGE and $PGF_{2\alpha}$ have no direct rate of effect when given into the dog sinus node artery[25] Furthermore at least $PGF_{2\alpha}$ enhances the response to nerve stimulation without changing responsiveness to norepinephrine or tyramine[26] and thus could conceivably occur with other prostaglandins and would enhance the cardiac rate response to nervous stimuli of reflex origin

The present study of the coronary circulation

Table I Systemic and coronary hemodynamic effects of intracoronary administration of PGE_1

Parameter	*Control*	*PGE_1 (8 7 mcg /min)*	*PGE_1 (21 4 mcg /min.)*
Heart rate (beats/minute)	105	117	132†
Mean arterial blood pressure (mm Hg)	132	123	111‡
Mean pulmonary arterial blood pressure (mm Hg)	15	15	15
Mean right arterial blood pressure (mm Hg)	4 4	3 9 †	3 7†
Arterial oxygen content (ml /100 ml blood)	17 4	17 9	17 9
Arterial mixed venous oxygen difference (ml /100 ml blood)	3 7	3 7	3 8
Coronary sinus oxygen content (ml /100 ml blood)	7 0	10 5 ‡	10 7‡
Cardiac output (L /minute)	3 35	3 49	3 50
Stroke volume (ml)	34	31	28
Left ventricular work (Kg M /minute)	6 1	5 8	5 4
Right ventricular work (Kg M /minute)	0 7	0 7	0 8
Total peripheral resistance (c g s units)	3 352	3 064	2 631‡
Total pulmonary resistance (c g s units)	401	378	377
Coronary sinus blood flow (ml /minute)	47	65‡	79‡
Coronary vascular resistance (units)	2 95	2 08‡	1 51‡
Left ventricular oxygen usage (ml /minute)	4 8	4 6	5 3

P < 0 05
†P < 0 02
‡P < 0 01

cent with PGE_2 and in the same dogs subsequent to propranolol administration it increased by 14 6 per cent This difference in response was significantly less (p<0 01) The decrease in coronary vascular resistance was significantly less also (p<0 02) while the change in coronary sinus blood oxygen content was comparable before and after propranolol induced beta blockade

Changes in response to intracoronary administration of PGE_2 before and subsequent to beta blockade by administration of sotalol are seen in Table IV There was a marked decrease in the change in heart rate with PGE_2 administration into the coronary artery after sotalol The increase in coronary blood flow with PGE_2 was less indeed it was no longer significant after sotalol, and coronary sinus blood oxygen content did not rise significantly Systemic arterial blood pressure tended to fall (p<0 05) more after sotalol however and the decrease in coronary vascular resistance with PGE_2 was comparable to that prior to sotalol administration No significant change occurred in the response of left ventricular oxygen consumption to PGE_2 after sotalol was given

In the determinations as to whether prostaglandins were more or less active than adenosine, when infusions were done consecutively into the same coronary artery it was established in two dogs that 50 mcg per minute of adenosine produced a response in coronary flow equivalent to that produced by 10 mcg per minute of PGE_1 In two dogs 100 mcg per minute of adenosine were equivalent to 10 mcg per minute of PGE_1 and in one dog 50 mcg per minute of adenosine produced the same response as 5 mcg per minute of PGE_1 Since the coronary response to PGE_1 and PGE_2 are shown here to be equal it is concluded that PGE_1 and PGE_2 are five to 10 times as potent per unit of weight in producing coronary vasodilatation as is adenosine

Discussion

The circulatory effects of PGA and PGE have recently been reviewed and it is generally agreed that they are vasodilators which decrease the peripheral resistance and systemic arterial pressure through relaxing vascular smooth muscle hence decreasing arteriolar resistance [1] PGF compounds tend to produce mild to moderate systemic arterial hypertension in chickens rats and dogs but apparently not in man [1]

Pulmonary arterial pressure tends to rise with administration of PGE PGA and PGF compounds [1] although the former two decrease and the latter increase pulmonary vascular resis

of the intact anesthetized dog confirms and extends previous reports of coronary vasodilatation by prostaglandins in the dog Thus PGA_1 has been reported to increase coronary blood flow significantly [2] or slightly [7] or actually reduce it if arterial pressure falls too far [9] In all cases however coronary vascular resistance decreases PGA_1 produced a transient mild increase in the coronary flow of open chest man when measured at thoracotomy for myocardial revascularization but the response was considerably less than that induced by papaverine [3] It was speculated previously that the anesthetized dog had too much coronary vasodilatation for PGA_1 to produce a significant further increase in coronary blood flow [3] Clearly this was not the case in the present study of PGE_1 and PGE_2, since when given into the coronary arteries of these intact anesthetized dogs there was a striking increase in coronary blood flow and coronary sinus oxygen content accompanied by a marked decrease in coronary vascular resistance This coronary flow response was still present but markedly reduced when beta receptor blockade was present. It should be noted, however that the change in coronary vascular resistance occurred undiminished after beta blockade but flow did not rise a comparable amount because of the reduced perfusing pressure

The changes in left ventricular oxygen consumption in the present study are minor and may be secondary to the increase in cardiac rate rather than to change in left ventricular work since cardiac work changes were unimpressive whereas the increase in cardiac rate tended to be quite striking prior to beta blockade and after beta blockade when the rate change was decreased there was no real change in left ventricular oxygen consumption Most of the coronary vasodilatation would appear to be produced by direct relaxation in vascular smooth muscle rather than by increased myocardial metabolic demand, because it still occurred in these present dogs with beta blockade when there was little rate change and because the coronary sinus oxygen content rose consistently supporting the idea that myocardial oxygenation is improved. As already indicated, prostaglandin compounds commonly increase contractility[8,23,24] and this would normally be expected to increase myocardial oxygen consumption [21]

Although adenosine is a very active coronary vasodilator it is of considerable interest that both PGE_1 and PGE_2 are considerably more active in this respect exceeding the efficacy of adenosine by 5 to 10 times per unit of drug weight. Since prostaglandins are naturally occurring potent vasoactive substances of ubiquitous distribution it is interesting to speculate as to their possible physiological role in the circulation as a whole As far as the heart is concerned, they are locally available rapidly destroyed, yet very effective coronary vasodilators consequently it is possible they have an important role in the local regulation of coronary blood flow This remains to be elucidated.

Summary and conclusions

1 PGE_1 and PGE_2 have been studied in anesthetized intact mongrel dogs before and subsequent to beta adrenergic blockade by propranolol and sotalol

2 Both of these prostaglandin compounds are active coronary vasodilators producing a considerable decrease in coronary vascular resistance and an increase in coronary blood flow

3 Although heart rate changed considerably with this manner of PGE_1 and PGE_2 administration systemic hemodynamic manifestations were minor The response in heart rate was reduced by propranolol and sotalol.

4 Minor or insignificant changes occurred in left ventricular oxygen consumption and the coronary sinus blood oxygen content rose

5 By comparison of vasodilation during intracoronary administration PGE_1 and PGE_2 are 5 to 10 times more effective per unit of weight than adenosine therefore they could be important in local regulation of coronary blood flow

Several compounds used in this study were graciously supplied by friends in the pharmaceutical industry Prostaglandin was supplied by Dr J E Pike and J R Weeks of the Upjohn Company Kalamazoo Mich. 49001 Propranolol was given by Dr R O Davies and associates of Ayerst Laboratories New York N Y 10017 Sotalol was supplied by Dr G R McKinney of Mead Johnson Research Center Evansville Ind. 47721 Dial urethane was furnished by C A Brownley Jr of CIBA Pharmaceutical Company Summit N J 07901

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Table III Systemic and coronary hemodynamic effects of intracoronary PGE_2 before and after propranolol

Parameter	Before propranolol		After propranolol	
	Control	PGE_2 (2 3 mcg /min.)	Control	PGE_2 (2 3 mcg /min.)
Heart rate (beats/minute)	112	118†	107	111
Mean arterial blood pressure (mm Hg)	127	121*	117	110‡
Mean pulmonary arterial blood pressure (mm Hg)	18	18	17	17
Mean right atrial blood pressure (mm Hg)	4 4	4 5	4 6	4 3
Arterial oxygen content (ml /100 ml blood)	17 5	17 5	17 6	17 2
Arterial mixed venous oxygen difference (ml /100 ml blood)	3 6	3 7	4 2	4 3
Coronary sinus oxygen content (ml /100 ml blood)	6 2	8 2‡	6 1	7 9‡
Cardiac output (L /minute)	3 71	3 67	3 11	3 41
Stroke volume (ml)	33	33	29	31
Left ventricular work (Kg M /minute)	6 4	6 3	4 9	5 1
Right ventricular work (Kg M /minute)	0 9	0 9	0 7	0 8
Total peripheral resistance (c g s units)	2 795	2 615	3 110	2 663
Total pulmonary resistance (c g s units)	387	378	453	399
Coronary sinus blood flow (ml /minute)	42	53‡	41	47‡
Coronary vascular resistance (units)	3 27	2 50‡	3 20	2 55‡
Left ventricular oxygen usage (ml /minute)	4 7	4 7	4 6	4 2

*P < 0 05
†P < 0 02
‡P < 0 01

Table IV Systemic and coronary hemodynamic effects of intracoronary PGE_2 before and after sotalol

Parameter	Before sotalol		After sotalol	
	Control	PGE_2 (6 mcg /min.)	Control	PGE_2 (6 mcg /min.)
Heart rate (beats/minute)	97	108†	98	99
Mean arterial blood pressure (mm Hg)	128	126	113	98
Mean pulmonary arterial blood pressure (mm Hg)	15	14	13	12
Mean right atrial blood pressure (mm Hg)	4 5	4 0	4 0	3 7
Arterial oxygen content (ml /100 ml blood)	17 4	17 4	17 9	17 6
Arterial mixed venous oxygen difference (ml /100 ml blood)	3 9	3 7	5 2	5 7*
Coronary sinus oxygen content (ml /100 ml blood)	5 1	7 9†	5 3	6 5
Cardiac output (L /minute)	3 10	3 60	2 53	2 56
Stroke volume (ml)	33	34	26	26
Left ventricular work (Kg M /minute)	5 4	6 2	4 0	3 7
Right ventricular work (Kg M /minute)	0 6	0 7	0 5	0 5
Total peripheral resistance (c g s units)	3 347	2 860	3 837	3 148
Total pulmonary resistance (c g s units)	391	331	418	406
Coronary sinus blood flow (ml /minute)	47	65†	36	40
Coronary vascular resistance (units)	2 75	2 02†	3 22	2 51†
Left ventricular oxygen usage (ml /minute)	5 8	6 0	4 5	4 4

*P < 0 05
†P < 0 01

Accelerated repolarization as a factor in re entry—stimulation of the electrophysiology of acute myocardial infarction

John Geddes M D *
M J Burgess M D **
Kay Millar M D
J A Abildskov M D
Salt Lake City Utah, and Belfast Northern Ireland

Slow intraventricular conduction has previously been shown to play a role in the genesis of re entrant arrhythmias[1] The study reported here demonstrates that localized areas with short recovery properties existing together with slow conduction enhance the likelihood of re entrant activity These two electrophysiologic abnormalities are both present early in the time course of acute myocardial infarction[2,3] and may contribute to the high incidence of ventricular arrhythmias during its early phases This report also provides evidence that the specialized ventricular conduction system may form part of the path for re entrant ventricular activity Such a role of the specialized conduction system has been demonstrated with isolated Purkinje muscle preparations[4,5] but has not been previously documented in intact hearts

Methods and materials

Experiments were performed on 18 mongrel dogs weighing 13 to 25 kilograms and anesthetized with intravenous pentobarbital 30 mg per kilogram The chest was opened with a sternal splitting incision and the heart supported in a pericardial cradle The sinus node was crushed and the right atrium driven at a basic cycle length of 500 msec In 12 experiments 5 mg of dibucaine were given intrathecally at the suboccipital level to permit control of the heart at the above rate

Thermal lesions were employed to alter electrophysiologic properties Recovery times were shortened by warming the surface of the ventricle and conduction time prolonged by cooling Loops of glass tubing covering an area 2 5 by 1 5 cm were sutured to the epicardium and water at controlled temperatures circulated through them The loops were placed on the left ventricle near the apex and on the anterior surface of the right ventricular wall It was necessary to separate the glass tubing in this way to avoid impairment of the mechanical activity of the ventricles The left ventricular site was cooled by water at temperatures down to 0 C circulated at a rate of 1 L per minute This area will be referred to as the coldspot The right ventricular site was warmed by the circulation of water up to 50 C at a rate of 0 5 L per minute This area will be referred to as the hotspot Five minutes were allowed to elapse after each temperature change before additional observations were made

The basic cardiac cycle was scanned with premature stimuli in decrements of 1 msec beginning from a time late in the cycle and the portion of the cycle during which re entrant beats occurred was noted. A digital stimulator with a

From the C rdiology Divisi n, D partm nt of M dic Un rsity f Utah College of Med ci Salt Lake C ty Utah, and th Cardiology Depa tme t Royal Victoria Hosp tal Groev or Rd., B lf st, Northern Irela d.

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Accelerated repolarization as a factor in re entry—stimulation of the electrophysiology of acute myocardial infarction

John Geddes M D *
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From the Cardiology Divis on, D partm nt of M dicin University of Utah Coll g of M d ne S lt Lake C ty Utah, and the Ca diology Department Royal Victoria Hosp tal Grosven Rd Belfast, North e Ireland.

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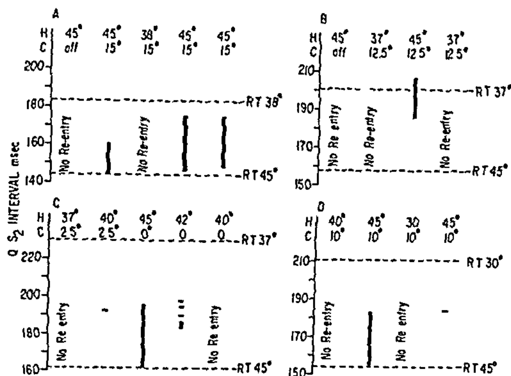


Fig 1 Graphs from four experiments of the intervals during which re entry occurred with a range of hotspot and coldspot temperatures The intervals from the onset of the QRS complex in response to the basic drive (Q) to the premature stimulus (S_2) that resulted in re entrant beats are indicated by the vertical bars. The temperatures employed are indicated at the tops of the graphs The dashed lines indicate the recovery times at the extremes of hotspot temperatures employed in each experiment The failure to elicit re-entry with a hotspot alone is illustrated in parts A and B In each experiment re entrant beats could be elicited by increasing the temperature of the hotspot in the presence of a coldspot which when present alone was not associated with re entry Fragmentation and finally disappearance of re-entrant beats with gradual decreases in hotspot temperature are seen in part C

timing accuracy of 0 1 per cent was used to deliver premature stimuli to a unipolar hook electrode In most instances the premature stimuli were delivered to the center of the hotspot on the right ventricle, but for certain purposes premature stimuli were delivered to the left ventricle 1 cm from the edge of the coldspot. Stimuli were 2 msec cathodal square wave pulses at three times diastolic threshold intensity and were delivered after every six basic drive cycles in most experiments and after every five cycles in the other experiments Ventricular responses to premature stimuli and beats in addition to those induced by the premature stimuli were observed on an oscilloscope or oscillograph Wallace and Mignone[1] have documented that re entrant beats can be elicited by premature stimulation in a similar preparation using a cold thermal lesion Selected recordings were made on a multichannel recorder using paper speeds of 25 to 100 mm per second In each experiment, an electrogram was recorded from a closely spaced bipolar electrode on the right atrium and a ventricular electrogram was recorded from hook electrodes arranged with the negative pole on the right and the positive pole on the left ventricle on an axis parallel to a line joining the hotspot and coldspot. The latter electrode configuration will be referred to as the biventricular lead. In certain experiments a multi electrode needle with 1 mm interelectrode distances was used to record electrograms from the left ventricle in or near the coldspot Additional electrograms from bipolar hook electrodes near the hotspot or coldspot were also obtained in some experiments

Results

Facilitation of re entry by the hotspot It was established that, with the range of warm temperatures employed re entrant activity could never be elicited by a premature stimulus in the presence of the hotspot alone However evidence that addition of a hotspot in the presence of a coldspot enhanced re entry was obtained under two conditions

In five experiments, a particular coldspot tem

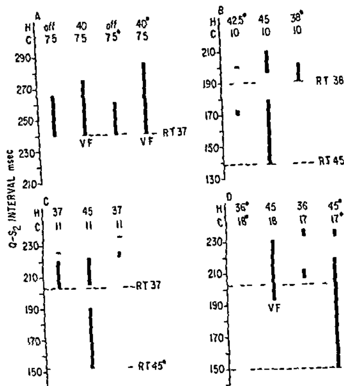


Fig 2. Graphs of the intervals of re entrant beats observed in four experiments. The format of these graphs is the same as that used in Fig 1 In these experiments a combination of hotspot and coldspot temperatures associated with re entrant beats was established. In each experiment increasing the hotspot temperature widened the Q S_2 interval during which re entry occurred and, in some instances ventricular fibrillation, indicated on the graphs by V F occurred with the early S_2

perature not associated with re entrant beats was established With the subsequent addition of a hotspot re entrant beats were elicited It is unlikely that these beats originated from pace maker cells whose automaticity was enhanced by the hotspot since they were never seen in the presence of the hotspot alone Data from four ex periments are illustrated in Fig 1 The vertical bars indicate the coupling intervals (Q S_2) of the premature stimuli which were followed by re en try The Q S_2 interval was timed from the onset of the last QRS complex in response to the basic drive (Q) to the premature stimulus (S_2) which elicited a response followed by additional beats which under the conditions of these experi ments are most likely re entrant beats The tem peratures of the hot and coldspots and recovery times at the extremes of hotspot temperatures used are indicated. Failure to elicit re entrant beats in the presence of the hotspot alone is il lustrated in parts *A* and *B* of Fig 1 In each ex periment increasing the temperature of the hotspot in the presence of a coldspot which was not associated with re entry resulted in one or more bands of Q S_2 intervals followed by re entrant beats With subsequent decrease in the hotspot temperature the re entrant beats disap peared. In the experiment illustrated in part C of Fig 1 gradual decreases in the hotspot temper ature produced fragmentation of the Q S inter vals followed by re entry and finally re entrant beats disappeared with further reduction of the hotspot temperature

In four additional experiments illustrated in Fig 2 a coldspot temperature or combination of hotspot and coldspot temperatures associated with re entry was established and the range of Q S_2 intervals followed by re entry observed. The hotspot temperature was then increased and re entry resulted over a wider range of Q S_2 inter vals indicating facilitation of re entry by the hotspot In the experiment illustrated in Fig 2 *A*, a coldspot temperature of 7 5 C in the absence of a hotspot permitted re entry to occur after Q S_2 intervals of 240 through 265 msec. The earliest effective stimulus did not result in multiple re

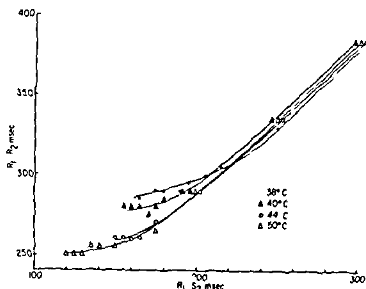


Fig 3 Graph of the relation of hotspot temperature and time of a premature stimulus delivered to the hotspot to activa *tion time at a site on the left ventricle near the coldspot* R_1 S_2 is the interval between activation at the left ventricular *site in response to the basic drive and delivery of the pre* mature stimulus to the hotspot R_1 R_2 is the interval between *activation of the left* ventricular site in response to the basic drive and activation at the left ventricular site in response to S_2 delivered *to the hotspot At all hotspot temperatures* tested there was a one to one relationship between R_1 R_2 and R_1 S_2 where the latter exceeded 240 msec At a hotspot temperature of 38 C R_1 S_2 intervals of less than 240 msec were *associated with less shortening of* R_1 R_2 *At warmer* temperatures the one to one relationship of R_1 S_2 and R_1 S_2 was maintained at shorter R_1 S_2 intervals

entrant beats or ventricular fibrillation With the addition of a hotspot at a temperature of 40° C the *range of Q* S_2 *intervals followed by re entry* widened to 240 through 275 msec and the earliest effective stimulus used resulted in ventricular fibrillation Reproducibility was dem onstrated by removing the hotspot which resulted in narrowing *the band of re entry and* the absence of ventricular fibrillation following the earliest effective *stimulus Addition of the* hotspot again widened the band of re entry and the earliest premature stimulus used again in duced ventricular fibrillation The increased range of Q S_2 intervals followed by re entrant beats *associated with increased temperature of* the hotspot is also illustrated in parts *B* C and *D* of Fig 2 The greater portion of the cycle during which re entry occurred included both Q S_2 inter vals scanned in the absence of the hotspot and the *shorter intervals* at which stimulation became possible in the presence of the hotspot

Since the time of delivery *of the premature* stimulus and the hotspot temperature both in fluenced the occurrence of re entrant beats the relation between hotspot temperature and ar rival time of premature impulses in the left *ventricle* was investigated *Fig 3* shows results of an experiment in which left ventricular activa tion time was studied as a function of S_2 timing and hotspot temperature *In this figure* R_1 *is the* activation time at a left ventricular site near the *coldspot following the basic drive* delivered to the atrium This time was measured from recordings taken from an intramural bipolar electrode S_2 *refers to the timing of the premature stimulus* delivered to the hotspot, and R_2 refers to the time of activation in response to S_2 at the left ventricu lar site R_1 S_2 intervals are shown on the abscissa and R_1 R_2 intervals are shown on the ordinate *Temperature of the hotspot did not influence the* one to one relation between R_1 R_2 and R_1 S_2 where the latter was in excess of 240 msec This *was not true of shorter* R_1 S_2 *intervals At a* hotspot temperature of 38° C, reducing R_1 S_2 *below 240 msec produced lesser degrees of shor* tening of R_1 R_2 However, at 50° C, the one to one relation was maintained down to an R_1 S_2 in terval of 180 msec Intermediate curves were ob tained at 40° C and 44° C It was apparent that *when the* S_2 *stimulus fell only shortly after the* end of the recovery time in the hotspot one effect of increasing the hotspot temperature was earlier arrival of the premature impulse in the left ventricle

***Activation order during re entrant* beats** It was noted in these experiments that the biventricu lar lead at times showed re entrant beats with positive QRS deflections suggesting origin in the right ventricle, negative deflections suggesting *origin in the left ventricle or biphasic deflections* of low voltage suggesting an intermediate origin *The variation in form of the re entrant beats* was independent of the combination of thermal le sions used Activation times in the right and left ventricles, near the thermal lesions were deter mined during the re entrant beats in three ex *periments In these* experiments in addition to the biventricular lead, pairs of closely spaced bipolar electrodes were *placed on the right and* left ventricles The results of experiments on two dogs are illustrated in Fig 4 In part *A* the form of the re entrant beat closely resembles the form of the beat in response to S_2 which was delivered to the right ventricle within the hotspot During the re entrant beat activation of the right

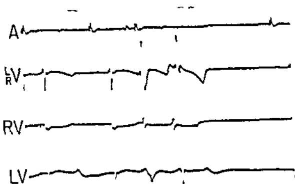


Fig 4A Electrograms of two dogs taken from the atrium (A) the biventricular lead (^L_RV) a bipolar electrode on the right ventricle near the hotspot (RV) and a bipolar electrode on the left ventricle near the coldspot (LV) In part *A* the first two complexes are in response to the basic driving stimuli the third complex is the response to S_2 and the fourth complex is a re-entrant beat In the biventricular lead, the form of the re entrant beat is similar to that of the S_2 induced beat and RV precedes LV activation In part *B* the first complex is the response to a basic driving stimulus the second complex is the response to S_2, and the next four complexes are re-entrant beats In the biventricular lead, the first re entrant beat is a narrow positive deflection and right precedes left ventricular activation The second re-entrant beat is a narrow negative deflection and right and left ventricular activation occur simultaneously The third and fourth re entrant beats are wide negative deflections and left precedes right ventricular activation

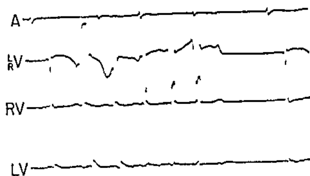


Fig 4B For legend see Fig 4 A

ventricle preceded activation of the left ventricle In another experiment illustrated in part *B* of Fig 4 S_2 was introduced within the hotspot on the right ventricle as in part *A* Multiple responses followed the S_2 induced beat In the biventricular lead the form of the first re entrant beat is a narrow positive deflection The electrograms from closely spaced bipolar electrodes on the right and left ventricles show that right precedes left ventricular activation The second re entrant beat is a narrow negative deflection and right and left ventricular activation occur simultaneously The third and fourth re entrant beats are wide negative deflections, and left precedes right ventricular activation The possibility that some of the complexes interpreted to be re entrant beats were in fact responses to retrograde atrial activity was considered. Fig 5 shows electrograms from one experiment in which S_2 was delivered simultaneously to the atrium and ventricle in some instances (top panel) and only to the ventricle in other instances (bottom panel) With both conditions of stimulation the re entrant beats at times had positive at times negative and at times biphasic forms in the biventricular lead.

In three experiments in which re entry was repeatedly produced by S_2 stimuli delivered over a range of times the activation times associated with the S_2 induced beat and the re entrant beat were determined at the right ventricular site near the hotspot and at a left ventricular site near the coldspot The intervals between the S_2 responses at the left ventricular site and the re entrant responses at the right ventricular site varied by 20 65 and 105 msec in the three experiments The intervals between the response to S_2 in the left ventricle and the re entrant response in the left ventricle however varied by only 5 25 and 55 msec When S_2 was delivered to the left ventricle near the coldspot rather than to the right ventricle near the hotspot the variations in intervals between S_2 re entrant responses at right and left ventricular sites were similar being 10 35 and 70 msec. for the right and 15 55 and 70 msec for the left ventricle In these three experiments re entry in the right ventricle always followed re entry in the left ventricle with a delay of 40 to 90 msec In any of the individual experiments the delay varied by only 5 to 20 msec These findings suggested that re entrant impulses originating in the left ventricle were propagated through it if it was excitable However if the left ventricular myocardium was refractory at the time the re entrant impulse originated, that impluse was transmitted to the right ventricle probably via the Purkinje net

Additional evidence that re entrant impulses emerged from the coldspot before transmission to

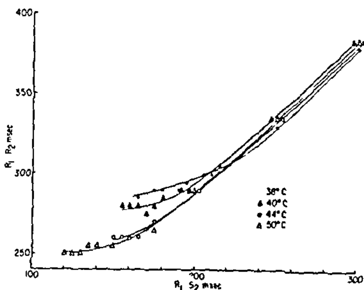


Fig 3 Graph of the relation of hotspot temperature and time of a premature stimulus delivered to the hotspot to activation time at a site on the left ventricle near the coldspot $R_1 S_2$ is the interval between activation at the left ventricular site in response to the basic drive and delivery of the premature stimulus to the hotspot $R_1 R_2$ is the interval between activation of the left ventricular site in response to the basic drive and activation at the left ventricular site in response to S_2 delivered to the hotspot At all hotspot temperatures tested there was a one to one relationship between $R_1 R_2$ and $R_1 S_2$ where the latter exceeded 240 msec At a hotspot temperature of 38 C $R_1 S_2$ intervals of less than 240 msec were associated with less shortening of $R_1 R_2$ At warmer temperatures the one to one relationship of $R_1 S_2$ and R_1-S_2 was maintained at shorter $R_1 S_2$ intervals

entrant beats or ventricular fibrillation With the addition of a hotspot at a temperature of 40° C, the range of Q S_2 intervals followed by re entry widened to 240 through 275 msec and the earliest effective stimulus used resulted in ventricular fibrillation Reproducibility was demonstrated by removing the hotspot which resulted in narrowing the band of re entry and the absence of ventricular fibrillation following the earliest effective stimulus Addition of the hotspot again widened the band of re entry and the earliest premature stimulus used again induced ventricular fibrillation The increased range of Q S_2 intervals followed by re entrant beats associated with increased temperature of the hotspot is also illustrated in parts *B C* and *D* of Fig 2 The greater portion of the cycle during which re entry occurred included both Q S_2 intervals scanned in the absence of the hotspot and the shorter intervals at which stimulation became possible in the presence of the hotspot

Since the time of delivery of the premature stimulus and the hotspot temperature both influenced the occurrence of re entrant beats the relation between hotspot temperature and arrival time of premature impulses in the left ventricle was investigated Fig 3 shows results of an experiment in which left ventricular activation time was studied as a function of S_2 timing and hotspot temperature In this figure, R_1 is the activation time at a left ventricular site near the coldspot following the basic drive delivered to the atrium This time was measured from recordings taken from an intramural bipolar electrode S_2 refers to the timing of the premature stimulus delivered to the hotspot, and R_2 refers to the time of activation in response to S_2 at the left ventricular site $R_1 S_2$ intervals are shown on the abscissa and $R_1 R_2$ intervals are shown on the ordinate Temperature of the hotspot did not influence the one to one relation between $R_1 R_2$ and $R_1 S_2$ where the latter was in excess of 240 msec This was not true of shorter $R_1 S_2$ intervals At a hotspot temperature of 38° C reducing $R_1 S_2$ below 240 msec produced lesser degrees of shortening of $R_1 R_2$ However at 50° C the one to one relation was maintained down to an $R_1 S_2$ interval of 180 msec Intermediate curves were obtained at 40° C and 44° C It was apparent that when the S_2 stimulus fell only shortly after the end of the recovery time in the hotspot one effect of increasing the hotspot temperature was earlier arrival of the premature impulse in the left ventricle

Activation order during re entrant beats It was noted in these experiments that the biventricular lead at times showed re entrant beats with positive QRS deflections suggesting origin in the right ventricle negative deflections suggesting origin in the left ventricle or biphasic deflections of low voltage suggesting an intermediate origin The variation in form of the re entrant beats was independent of the combination of thermal lesions used Activation times in the right and left ventricles near the thermal lesions, were determined during the re entrant beats in three experiments In these experiments in addition to the biventricular lead pairs of closely spaced bipolar electrodes were placed on the right and left ventricles The results of experiments on two dogs are illustrated in Fig 4 In part *A* the form of the re entrant beat closely resembles the form of the beat in response to S_2 which was delivered to the right ventricle within the hotspot During the re entrant beat activation of the right

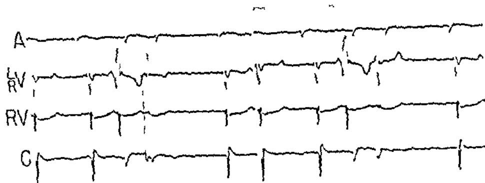


Fig 6 Electrograms from the atrium the biventricular lead a bipolar electrode on the right ventricle and a bipolar intramural electrode in the subendocardium of the left ventricle near the coldspot (C). The photographs have been retouched to show the spikes. In the panel on the left in the biventricular lead the re-entrant beat is a narrow upright deflection indicating origin in the right ventricle In the electrogram from C, the re entrant complex has a wide triphasic form with the first spike preceding and the second spike following right ventricular activation. In the panel on the right, in the biventricular lead, the re entrant beat is a narrow negative deflection indicating origin in the left ventricle The electrogram from C has a monophasic form and precedes right ventricular activation

dial electrograms and still later fibrillation was apparent in the biventricular lead. Waldo and Kaiser[6] have reported the occurrence of local fibrillation in ischemic areas in dogs with acute coronary ligation.

Discussion

The experimental model employed in this study includes two major electrophysiologic abnormalities present in myocardial infarction Slow conduction velocity after experimental coronary ligation has been demonstrated by Durrer and co-workers[2] and reduction of recovery time by acute ischemia is well established. The model differs from actual ischemia in other respects and the possible role of these differences in relation to re entrant arrhythmias has not been defined. Despite differences between actual ischemia and the thermal lesion model it is likely that arrhythmias in the two are related Both are localized lesions in which conduction velocity and recovery time have been altered, and both include the specific alterations of prolonged conduction and reduced recovery times While localized cooling prolongs recovery time as well as decreasing conduction velocity it has been previously shown that prolonged conduction is the necessary condition for re entry with such a lesion Since re entrant beats could be elicited in the presence of the coldspot alone but not in the presence of the hotspot alone the findings of this study suggest that prolongation of conduction time plays a more important role in the occurrence of re entrant arrhythmias than reduction of recovery time However re entrant activity was enhanced by shortening recovery times The mechanism by which shortening of recovery time enhances re entry has not been completely defined but possible mechanisms can be suggested. Since warming permitted earlier right ventricular responses than were otherwise possible the consequent left ventricular activation was more premature in the presence than in the absence of localized warming It was therefore likely that left ventricular tissue was less completely recovered, activation fronts were more fragmented, and re entry enhanced. It is also possible that delayed conduction at the boundary of the warm lesion and normal myocardium produced an irregular activation front which summated with that produced by the cold lesion to fragment excitation and led to re entry In addition it is theoretically possible that the warm lesion facilitated re entry by reducing recovery time but via the mechanism of making the right ventricle available for the re entrant beat when other areas were refractory This seems unlikely since even those re entrant beats which appeared first in the right ventricle emerged in unwarmed portions as early as in the warm area These experiments do not however, exclude such a mechanism in actual ischemia

The unexpected sequence of activation noted during some of the re entrant beats must involve

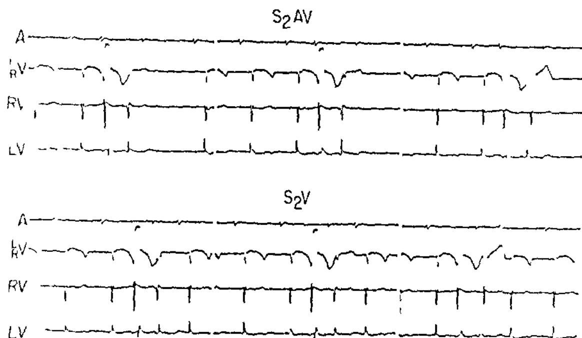


Fig 5 Electrograms from the atrium biventricular lead and the right and left ventricles In the upper panel S_2 was delivered simultaneously to the hotspot on the right ventricle and to the right atrium In the lower panel S_2 was delivered only to the right ventricle With both conditions the re entrant beats had positive negative and biphasic forms indicating that the waveform of the re-entrant beat was unrelated to the timing of atrial activation

the right or propagation through the left ventricle was obtained in two experiments In these experiments electrograms were recorded from a bipolar electrode placed in the subendocardium immediately beneath the coldspot Electrograms from one of these experiments are shown in Fig 6 In the panel on the left the re entrant beat recorded from the biventricular lead was a positive deflection suggesting origin in the right ventricle During this re entrant beat the electrogram from the left ventricular subendocardial electrode was wide and had a triphasic form The interval between S_2 and the beginning of this complex was less than the interval between S_2 and the beginning of the monophasic left ventricular complex shown in part *B* of Fig 6 and preceded activation in the right ventricle The last spike of the triphasic complex followed right sided activation These findings are compatible with a local re entrant impulse originating in the subendocardium of the left ventricle and finding accessible left ventricular tissue refractory spreading to the right ventricle via the specialized conduction system before activating the remainder of the left ventricle In the panel on the left, the re entrant beat recorded from the biventricular lead is a negative deflection suggesting origin in the left ventricle The electrogram from the subendocardial left ventricular electrode is monophasic and activation at this site precedes right ventricular activation This suggests that this slightly later re entrant impulse encountered excitable left ventricular myocardium and immediately spread through the left ventricle

In another experiment illustrated in Fig 7 it was noted that when multiple re entrant beats induced ventricular fibrillation disorganized activity appeared in the coldspot before fibrillation of the entire ventricle was apparent In the upper panel a short run of ventricular tachycardia which terminated spontaneously is apparent in the biventricular lead The electrogram from the subepicardial lead near the coldspot shows disorganized activity while discrete QRS complexes were recorded from a subendocardial site beneath the coldspot The tracings in the lower panel were recorded shortly after those in the upper panel During this tracing ventricular tachycardia deteriorated into fibrillation of the entire ventricle As in the upper tracing disorganized activity appeared first in the epicardial electrogram Later, disorganized activity was recorded in both the epicardial and subendocar

Epicardial mapping and surgical treatment in Wolff Parkinson White syndrome Type A

Hein J J Wellens
Michiel J Janse*
Rudolf Th Van Dam*
Frans J L van Capelle
Nico G Meijne*
Heleen M Mellink**
Dirk Durrer*
Amsterdam, The Netherlands

The mapping of epicardial excitation both during sinus rhythm[1] and tachycardia[11] and the use of electrical stimulation of the heart[2] has led to a better understanding of the Wolff Parkinson White syndrome By way of these techniques it has been demonstrated that an anomalous atrio ventricular bypass frequently plays a crucial role in the arrhythmias in these patients This knowledge has opened new ways of treatment for those patients who are severely crippled by their arrhythmias and cannot be controlled by drug treatment

This report describes our experience in four patients with Wolff Parkinson White syndrome Type A where surgical intervention was nec essary because of failure of drug therapy

Material and methods

Table I lists the characteristics of the four pa tients studied. It should be noted that in two of our patients (A and C) the combination of rheumatic heart disease and frequent episodes of atrial fibrillation and flutter with rapid ventricu lar rate leading to severe congestive heart failure was the indication for surgical therapy

From the Departm nt of C rdiology a d Cl n cal Phy ology and the Dep rtment of Ca d ovasc l r S rgery W lh lm na G sthuis Un rsity of Amsterdam, The Neth lands.

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Repri t requests to Dr H in J J Wellens Department f Card logy nd Clinic l Physiology Wilh lmi Gasthuis, Univers ty of Amster dam The Neth la ds

D p rtme t of Card ology and Cl ical Phys logy Uni ers ty of Amste dam

Departm nt f Cardiovascular Surg ry Un rsity of Amste dam.

Patient B had to be treated repeatedly by car dioversion because of the high ventricular fre quency during tachycardia leading to severe angina and cardiac shock

In patient D the tachycardias could not be controlled by digitalis pronestyl β blocking agents and diphenylhydantoin given singly or in combination In all four patients left and right heart hemodynamic studies and electrical stim ulation studies were performed prior to surgery The latter were done with patients during sinus rhythm The results of the stimulation studies can be summarized as follows

Increase in pre excitation following premature atrial beats Using the extra stimulus method[2] we found that all patients showed an increase in pre excitation on decreasing the atrial pre mature beat interval during driving of the atrium at a regular rate The His bundle elec trograms during this procedure showed the characteristic increase in time between begin ning of ventricular activation by way of the ac cessory pathway and activation of the His bun dle[3] In patients A B and D where right and left atria were driven at identical frequencies pre excitation was more pronounced during driving of the left atrium[4] An example is shown in Fig 1

Initiation and termination of tachycardias In patient A a circus movement tachycardia could be initiated by a single left atrial or left ventricu lar premature beat and by two right ventricular premature beats given in close succession Tachycardias could be terminated by one early left atrial and left ventricular premature beat

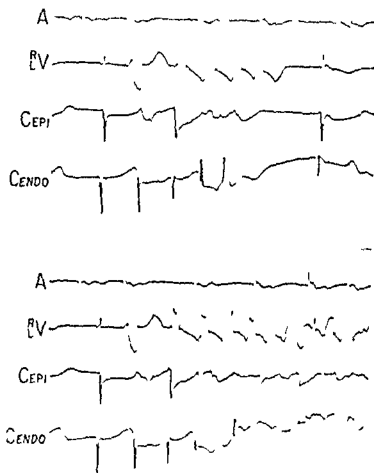


Fig 7 Electrograms from the atrium the biventricular lead a bipolar electrode on the epicardium near the coldspot (C_{EPI}) and a bipolar lead on the endocardium beneath the coldspot (C_{ENDO}) The photographs have been retouched to show the spikes In the upper panel S_2 is followed by multiple re entrant beats Disorganized activity was recorded from C_{EPI} while discrete spikes were recorded from C_{ENDO} In the lower panel the multiple re entrant beats that followed S_2 deteriorated to ventricular fibrillation Disorganized activity appeared first in C_{EPI} then in C_{ENDO} and finally in the biventricular lead

the specialized conduction system The Purkinje system is known to have a long recovery time If the distal portion of that system was refractory at the time of the induced premature beat it would then be available for excitation by a re entrant impulse Such local block within this system during premature beats has been demonstrated by Myerburg Gelband and Hoffman[4] and by Anderson, Greenspan and Bondura[5]

The findings of this study demonstrate that shortening of recovery time which is a feature of very early ischemia enhances re entrant activity This electrophysiologic feature of early ischemia together with other arrhythmogenic factors may be responsible for the high incidence of ectopic ventricular activity in the early phases of acute myocardial infarction Local block of the Purkinje system in early infarction may also play a contributory role in re entrant ectopic activity

Summary

A laboratory animal model employing thermal lesions was developed to demonstrate that re entrant activity made possible by prolongation of conduction time could be enhanced by shortening of recovery properties Cooling was used to prolong conduction time and warming to shorten recovery time The cardiac cycle was scanned with premature stimuli of three times diastolic threshold intensity Re entrant activity could not be elicited in the presence of shortened recovery times alone However, abbreviation of recovery time enhanced re entrant activity, permitting re entrant beats to occur during a greater period of the cardiac cycle and to occur at cold temperatures that when present alone were not associated with re entry During some re entrant beats, right preceded left ventricular activation despite evidence that re entrant activity originated in the left ventricle in the area of the cold spot. This was an unexpected finding and suggested that the Purkinje net played a role in the re entrant loop The findings of this study indicate that while prolongation of conduction time is necessary for re entrant activity it is enhanced by shortening of recovery times Both of these electrophysiologic features are present in the early phases of acute myocardial infarction and may be a factor in the very high incidence of ventricular ectopic activity at that time

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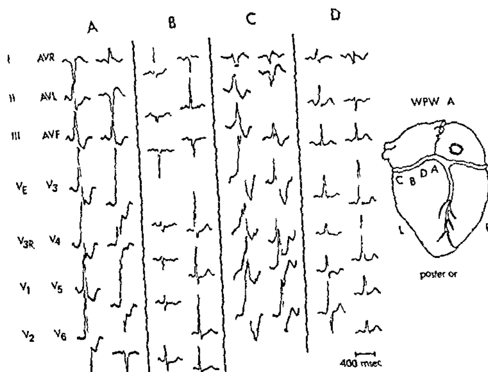


Fig 2 Preoperative electrocardiograms of patients A B C and D The drawing on the right shows the sites of earliest epicardial ventricular excitation during pre-excitation

Exploration of ventricular excitation The methods of recording epicardial and intramural leads have been described previously [5]

Briefly after opening the pericardium unipolar and bipolar complexes were recorded using a hand held electrode carrying two silver electrode terminals of 0 1 mm diameter with an interelectrode distance of 1 mm The locations of recording sites were entered on drawn maps of the ventricular surface The signals were recorded simultaneously with a constant unipolar reference tracing taken from a plunge electrode placed into the left ventricular cavity and a standard lead of the electrocardiogram in which a delta wave could be identified. All complexes were recorded from a high fidelity four channel oscilloscope on 36 mm film at a speed of 6 4 cm per second. During the operation in order to determine which site on the ventricular surface was activated early the complex recorded with the exploring electrode and a reference complex were displayed on a slave two channel oscilloscope If sinus rhythm was present, this oscilloscope was triggered by a complex recorded from the atrium In the presence of atrial fibrillation it was triggered by the ventricular reference complex Although exact measurements of activation times could not be made the area of earliest activation could be localized by constantly monitoring these two complexes on the oscilloscope screen during the procedure For the final time measurements the recordings were enlarged to such an extent that 1 mm corresponded to 1 msec The rapid part of the intrinsic deflection from the unipolar complex, signalled the arrival of the excitation wave in the subepicardial layer in contact with the exploring electrode [6]

Results

Patient A She was operated upon for the first time on March 14 1969 Shortly after the induction of anesthesia the patient went into atrial fibrillation This resulted in a varying degree of pre excitation individual ventricular complexes ranged from narrow QRS complexes (His conduction) to QRS complexes beginning with a delta wave (fusion complexes between normal and anomalous A V conduction) or A V conduction exclusively via the anomalous pathway After

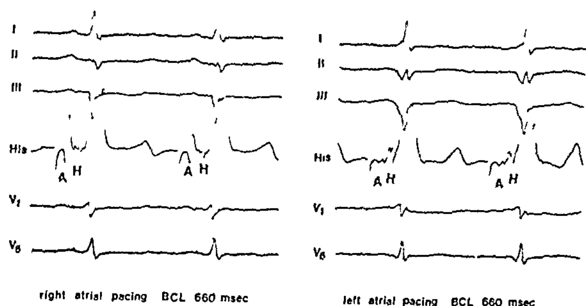


Fig 1 Standard electrocardiogram leads and His bundle electrogram during stimulation on the right and left atrium at basic cycle length (BCL) 660 msec Note the increase in pre excitation when the left atrium is stimulated

Table I

Pat	*A*	*A*	*B*	*C*	*D*
Sex	Female		Female	Male	Female
Age (years)	49	51	58	31	27
Type tachycardia	C M A fibr A fl	C M A fibr A fl	C M	C M A fibr A fl	C M
Additional abnormalities	*M S slight M I* P H	*Severe M I* P H	*C A D*	*M S M I* P H	–
Indication operation	Tachycardia+ valve lesion	Same	High rate tachycardia (220/min) angina shock	Tachycardia+ valve lesion	Tachycardia
Operation	Diss A P Commissurotomy M V	Diss His + A P M V replacement P M impl	Diss His P M impl	Diss. His + A P M V replacement P M impl	Diss His P M impl

Abbreviations C M = circus movement, A fibr = atrial fibrillation, A fl = atrial flutter M S = mitral stenosis, M I = mitral incompetence, P H = pulmonary hypertension C A D = coronary artery disease A P = anomalous pathway M V = mitral valve P M = pacemaker Diss = dissection

In patient B after a single right atrial or right ventricular premature beat failed to initiate a tachycardia a tachycardia was initiated by a single left atrial premature beat When during the tachycardia, an early left atrial premature beat was given atrial fibrillation supervened with a very high ventricular rate (approximately 300 per minute) In view of the rapid deterioration of the circulatory status following this arrhythmia, she was cardioverted and the catheterization terminated

In patient C, circus movement tachycardias were initiated by a single right ventricular premature beat Left sided stimulation was not done Both a right atrial or a right ventricular premature beat ended the tachycardia

In patient D circus movement tachycardias could be initiated and terminated by a single premature beat from the right or left atrium Right ventricular premature beats did not terminate the tachycardia left ventricular stimulation was not performed

The electrograms of all four patients prior to surgery are shown in Fig 2

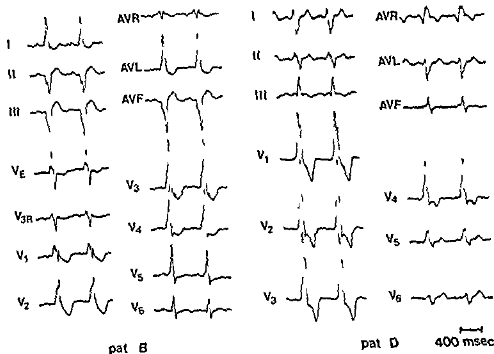


Fig 3 Postoperative electrocardiograms of patients B and D showing ventricular activation occurring exclusively by way of the accessory pathway

complex configuration following electrically induced atrial premature beats or during pacing of the left and right atrium at identical driving rates.

Patient C Like patient A this patient was completely crippled by the combination of severe rheumatic mitral valve disease paroxysmal atrial fibrillation and Wolff Parkinson White syndrome The patient was operated upon on Dec 14 1971

Epicardial excitation mapping was hampered by the presence of atrial fibrillation consequently QRS complexes varied between those showing A V nodal propagation (narrow) and complete pre excitation (wide QRS) Local epicardial excitation times following the earliest discernable ventricular activation during maximal pre excitation are assembled in Fig 4 The area of pre excitation was localized on the high posterobasal aspect of the left ventricle (10 *to* 15 msec. after the beginning of positive deflection of pre excitation complexes) Following the identification of that area the same approach was followed as during the second operation in patient A Again sutures in the area of A V node and His bundle resulted only in the appearance of exclusive pre excitation complexes With the patient on extracorporeal circulation and in ventricular fibrillation the mitral valve was removed and replaced by a Starr Edwards ball valve prosthesis

An extra line of sutures was placed above the valve ring in the area between the mitral valve annulus and the aortic root Following defibrillation total heart block was present with narrow QRS complexes Thereafter a demand pacemaker was inserted The postoperative course was complicated by sepsis with *Pseudomonas aeruginosa*. This responded to antibiotic therapy

At present 23 months following operation he is working full time as a secondary school teacher Total heart block is still present as shown during pacemaker suppression

Patient D Patient D was operated upon Sept. 19 1972 The problem in this patient was circus movement tachycardia which could not be controlled by drug treatment It was decided to interrupt the His bundle only Epicardial mapping was not carried out in great detail and was concentrated on the posterior surface of the left ventricle

It was found that a very small area just to the

the pericardium was opened, it was tried unsuccessfully to cardiovert the arrhythmia Excitation mapping was seriously hampered by the presence of QRS complexes continuously changing in configuration and by premature beats evoked by the exploring electrode In spite of this difficulty we thought that we could locate the earliest area of left ventricular epicardial activation high on the posterobasal part of the left ventricle, close to the posterior descending coronary artery (Fig 2) In this area, the earliest epicardial excitation occurred about 20 msec following the beginning of the left ventricular cavity complex Thereafter, with the patient on extracorporeal circulation the left atrium was opened a commissurotomy performed and a 6 cm long endocardial incision was made along the posterior wall of the left atrium just above the atrioventricular ring Following the operation the patient had exclusive conduction by way of the His bundle for 72 hours Then, however, conduction by way of the anomalous connection recurred The first year following operation the patient had only four short episodes of tachycardia that responded rapidly to drug therapy She then started to have paroxysmal atrial fibrillation with high ventricular frequency that could not satisfactorily be controlled Two and a half years following operation the patient was readmitted in severe heart failure The electrocardiogram showed atrial fibrillation with a ventricular frequency of 160 to 200 per minute Most of the QRS complexes showed pre excitation Digitalis and excessive doses of pronestyl (10 Gm daily) brought the ventricular frequency in an acceptable range (70 to 100 per minute) her circulatory status however deteriorated Cineangiography from the left ventricle showed grade 3/4 mitral regurgitation The cardiac index was 1 81 per minute per square meter The pressure in the pulmonary artery at rest 40/10 mm Hg, rose on slight exercise to 90/30 mm Hg

She was reoperated on Dec 9, 1971 Pericardial adhesions prevented mapping of epicardial excitation After opening the right atrium a number of sutures were placed in the area of the A V node and His bundle This resulted in a change from QRS complexes showing A V conduction over the His pathway the accessory pathway and both pathways to only wide QRS complexes preceded by a large delta wave Subsequently, the patient was placed on extracorporeal circulation ventricular fibrillation initiated and the interatrial septum opened

The mitral valve was removed and replaced by a Starr Edwards prosthesis Thereafter, six more sutures were placed in the atrial septum immediately above the atrioventricular ring Following closure of the interatrial septum the patient was defibrillated She showed complete heart block with narrow QRS complexes indicating that the site of origin of the ventricular complexes was the bundle of His Epicardial electrodes for a demand pacemaker were sewn upon the left ventricle The postoperative course was uneventful At present (23 months postoperatively) she has not shown recurrence of pre excitation and has fully resumed her household activities The electrocardiogram shows a pacemaker rhythm Suppression of the demand pacemaker by chest wall stimulation[18] reveals a total heart block with narrow QRS complexes, with a frequency of 50 per minute

Patient 8 As described above the problem with this patient was circus movement tachycardias occasionally deteriorating into atrial fibrillation with high ventricular rate, leading to severe angina and low output failure She was operated upon on Feb 12 1970 Epicardial excitation mapping was performed on 41 sites located on both ventricles during sinus rhythm and regular driving of the right and left atrium at a frequency slightly higher than during sinus rhythm As shown in Fig 2 an area of early ventricular excitation was found on the posterobasolateral aspect of the left ventricle The area increased in size during left atrial pacing The configuration of the QRS complexes (Fig 2) suggested that the anomalous bundle probably was located close to the posterior fascicle of the left bundle

In view of these findings with the patient on extracorporeal circulation the right atrium was opened and sutures placed in the region of the A V node and His bundle This resulted in complete heart block An on demand pacemaker with epicardial electrodes was implanted and the operation terminated As demonstrated by the pacemaker suppression method[18] a complete A V block was present till four days postoperatively Then atrioventricular conduction reappeared probably by way of the anomalous connection only as shown in Fig 3 This was confirmed later by showing that there were no changes in QRS

pathway is not always located epicardially Under these circumstances epicardial excitation mapping is obviously not the answer for exact location of the bypass. If an intramural or endocardial bypass is present several factors play a role in the pattern of epicardial activation like (A) thickness of the ventricular wall and (B) the site of the ventricular end of the accessory pathway in relation to the specific conduction system If as pointed out by Myerburg Nilsson and Gelband,[17] the impulse gets ready access to the specific conduction system the pattern of ventricular activation will be different as compared to the situation where the anatomic location of the bypass prevents this from occurring [18]

(4) The left ventricular cavity potential the beginning of which we generally used as a zero time reference as to the onset of left ventricular activation is changed markedly during pre excitation Instead of the Q wave present during pure His activation a small R appears and the occurrence of intrinsic deflections in the earliest area of left ventricular pre excitation may even preceed the slow onset of this low voltage R wave which also is subject to positional changes of the heart.

To reduce some of these difficulties we now prefer to have as a fixed time reference a signal carrying an easily recognizable intrinsic deflection recorded from an intramural terminal of a needle electrode inserted into the left ventricular wall The time relations between this complex and the signals recorded from the exploring electrode are instantly available The exact relationship with the left ventricular cavity potential can be worked out during the final analysis which is done after the operation To differentiate between epicardial intramural or subendocardial insertion of the bypass a needle should be inserted into the area of earliest epicardial activation and the intramural spread of activation determined. The special problems which occur when atrial fibrillation is present will be dealt with in a separate paper

So far the accessory bundle has defied exact localization in its entire course It has been shown in patients with Wolff Parkinson White Type B that their anomalous pathway was a direct connection between the right atrium and the lateral aspect of the right ventricle where the earliest activated region could be readily located by epicardial mapping [1 9 11] Successful dissection of this connection by way of a lateral incision in Wolff Parkinson White Type B has been performed three times by the group of Wallace and co workers [9] and once by our group Unsuccessful attempts were reported by Burchell and co workers [11] Cole and co workers [12] and Lindsay and co workers [13] Fontaine and co workers[10] described an extremely interesting patient in whom the electrogram was intermediate in type between A and B The accessory pathway was successfully interrupted by numerous sutures on the posterolateral aspect of the right ventricle close to the A V sulcus

So far no other reports have appeared describing successful interruption of the anomalous pathway in Wolff Parkinson White Type A by way of a lateral incision

As previously outlined in two of our four patients we had to dissect the anomalous pathway because during atrial fibrillation high ventricular rates resulted from conduction over this connection The observations listed above the disappearance of pre excitation for four days following ligature of the area of A V node and His bundle in patient B and the results of our stimulation studies in patients with Wolff Parkinson White Type A [4] made us decide to use the following approach during the second operation in patient A and in patient C Since we believed that the anomalous pathway was most likely situated close to the A V junction we started by interrupting the A V node and His pathway by sutures This however only resulted in disappearance of fusion complexes and the emergence of pure pre excitation complexes

Then (1) the atrial septum was opened and the mitral valve replaced by a Starr Edwards ball valve prosthesis and (2) an extra line of sutures was placed closely above the mitral annulus going both anteriorly and dorsally toward the aortic root These procedures in the left atrium were done with the patient on bypass and the heart in ventricular fibrillation therefore the exact location of the anomalous pathway interrupted by the sutures could not be identified.

As reported above both patients have not shown recurrence of conduction over the anomalous bypass for the past 20 months Since complete heart block was produced, both patients had a demand pacemaker implanted.

Several authors[20-23] have pointed to the many connections that can be present between the

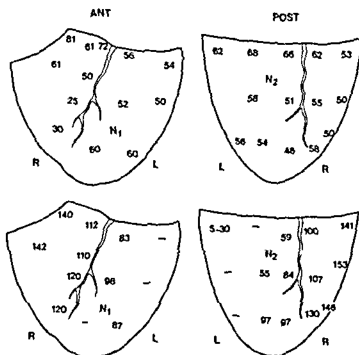


Fig 4 Epicardial excitation maps from patient C Top activation via the His bundle only Bottom activation during maximal pre-excitation All excitation times are in milliseconds following the onset of the left ventricular cavity potential

left of the descending coronary artery and directly below the atrioventricular sulcus, was activated 2 msec before the beginning of the left ventricular cavity potential If the recording electrode was moved over a small distance (1 cm) activation times were 10 to 20 msec later Several sutures were placed in the area of the atrioventricular node and bundle of His This resulted in a further widening of the QRS complexes from 130 msec to 180 msec, indicating that A V conduction occurred only via the anomalous bypass Postoperative stimulation studies showed no differences in QRS complex configuration following pacing of the right and left atrium at identical basic driving rates and premature beat intervals, indicating that A V conduction occurred via the accessory pathway only The postoperative electrocardiogram is shown in Fig 3

Discussion

As recently pointed out by Burchell [7] only a very limited number of patients with the Wolff Parkinson White syndrome need surgical therapy In patients in whom stimulation studies demonstrate that the A V node is an essential link in the tachycardia circuit, dissection of the A V node or His bundle and prophylactic implantation of an on demand pacemaker, as suggested by Dreifus and co workers,[8] is a sensible therapeutic approach This procedure resulted in complete cure from tachycardias in our patients B and D If stimulation studies have demonstrated that the refractory period of the accessory pathway is not a very short one, interruption of the bundle of His seems to be the operation of choice in patients with Wolff Parkinson White Type A and circus movement tachycardias However, the situation is completely different when the problem consists of supraventricular tachycardias like atrial flutter or atrial fibrillation with atrioventricular conduction over an anomalous pathway with a short refractory period

In these cases, the anomalous pathway has to be interrupted In order to dissect this connection one has to locate it. If the accessory pathway is located epicardially, the ventricular insertion can be found by locating the earliest activated area on the ventricular surface during pre excitation by way of epicardial mapping The atrial end can be found by recording atrial activation when ventriculo atrial conduction via the anomalous bundle is present as is the case during circus movement tachycardia[11] or in approximately 60 per cent of patients during ventricular pacing [19] During epicardial mapping in the Wolff Parkinson White syndrome, we have met with several technical and electrophysiological difficulties that could not all be solved during the time available for electrophysiological exploration

(1) Phenomena used as criteria for assessing the presence and degree of pre excitation may change to such an extent during and as a result of the surgical conditions that their reliability is greatly diminished This applies in particular to the standard lead electrocardiograms when the heart is luxated in order to explore the posterior and postero inferior surface which is the most important area in Wolff Parkinson White Type A, standard leads may become unrecognizable and the presence of delta waves may be hard to establish

(2) Probably due to the pharmacologic effect of the agents used for anesthesia pre excitation may be greatly diminished or even abolished, at operation, in one case we had to produce pre excitation by the administration of digitalis which in that particular patient was known to enhance pre excitation [34]

(3) As suggested by our patient B, the accessory

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Patients A C and D show a similarity in their electrocardiograms during maximal pre excitation The configuration of the QRS complex is in agreement with ventricular activation spreading from the posterobasal region of the left ventricle On the epicardial surface however the earliest point of activation in patient C was located approximately 7 cm to the left as compared to patient A The configuration of the QRS complex from patient B is different from the others

In view of the QRS complex during pre excitation we think that in this patient ventricular activation might have started in the region of the posterior fascicle of the left bundle The location of the earliest point of activation on the epicardium in this patient, however was very close to that of patient C As described by Lewis[33] and recently demonstrated by Myerburg Nilsson and Gelband [17] the pattern of ventricular excitation is influenced by the ability of an ectopic impulse to enter the specific conduction system

Absence of the latter in the posterobasal area of the left ventricle might have resulted in the rather uniform QRS configuration during maximal pre excitation in patients A C and D Our studies indicate that a systematic search for the effect of site and timing of ventricular pre excitation on QRS complex configuration is essential for understanding of the electrocardiographic patterns Epicardial mapping of the ventricular surface alone does not give sufficient information to solve this problem

Summary

Epicardial excitation mapping was performed in four patients with the Wolff Parkinson White syndrome Type A In all patients the earliest epicardial excitation times were found to be located on the postero baso lateral part of the left ventricle In two patients, both suffering from incontrollable atrial fibrillation in the presence of rheumatic mitral valve disease the accessory pathway was successfully interrupted along with ligation of the bundle of His and replacement of the mitral valve In the other two patients the His bundle was interrupted by sutures All patients did extremely well following surgery Both the value of and the problems encountered during epicardial excitation mapping in the Wolff Parkinson White syndrome are discussed. The conclusion is reached that mapping of the ventricular epicardium alone usually does not allow identification of the exact course of the accessory pathway It gives only a partial answer in our search for understanding the relation between ventricular excitation and QRS complex configuration in patients with the Wolff Parkinson White syndrome

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atrium and ventricle and might lead to pre ex citation of the ventricle

Schematically they have been grouped as (1) *true atrioventricular connections* outside the A V junction (the so called bundle of Kent) (2) connections between the A V junction (A V node and His bundle) and the ventricle (Mahaim fibers), (3) fibers that bypass an important part of the A V junction, but that insert into the tail of the A V node (James bundle) and (4) combinations of 1 2 and 3 *Especially the latter situation*, which may result in identical QRS complexes as *during a true A V nodal bypass* can make surgical intervention unsuccessful Therefore in the workup of patients in which surgical therapy is considered necessary as much information as possible as to the location of the anomalous bypass track(s) should be assembled.

As outlined elsewhere [24] this has led us to follow *a certain protocol in these patients* The disappearance of pre excitation following procedures around the mitral valve ring in our patients A and C, calls for a discussion of observations of specific conduction tissue in the proximity of the A V ring

Truex Bishof, and Hoffman[25] found an accessory atrioventricular muscle bundle of the developing heart close to the A V junction in between the mitral valve ring and the aortic root

Robb and Petri[26] described that in human fetal *hearts specialized tissue was related to the en*tirety of the primitive atrioventricular junction Very recently *Anderson*[27 28] and *Anderson and* Taylor[29] did find rings of specialized tissue around the A V orifices in guinea pig human fetal hearts and rat and rabbit hearts These observations suggest that pre excitation might result from remnants of these rings of specialized tissue around the A V valves and that the location of the anomalous pathway might differ, depending upon what part of the ring remains James[30] has denied the presence of remnants of these rings of specialized tissue in the human heart Even if remnants of these rings can be found in the human heart one still has to prove their func*tional significance* as far as impulse conduction is concerned Like Boineau and co workers [14] we are extremely *interested in the relation* between the pattern of ventricular excitation and the QRS complex *configuration during pre excita*tion In contrast to these authors however we consider the QRS complex *during sinus rhythm* an unreliable guide to the area of pre excitation *The difficulty* in predicting the site of ventricular insertion of the bypass in patients with the Wolff Parkinson White syndrome is that ventricular activation usually occurs by two pathways The contribution to ventricular activation by bypass will not only differ from patient to patient but also in the same patient depending upon (1) the *distance between the site of supraventricular im*pulse formation and the A V node and atrial end of the bypass and the time required to bridge these distances [14] (2) Transit time in the bypass (probably related to the thickness of the accessory bundle) vs transit time through the A V junction (3) The location of the bypass (endocardially, epicardially, or intramurally), its proximity to the specific conduction system and the ability of *the impulse to invade this system*

Other factors which will influence the QRS *complex configuration in patients with the Wolff* Parkinson White syndrome will be ventricular *hypertrophy, fibrosis intramural block* and bundle branch block To us under these circumstances prediction of the site of ventricular insertion of the bypass during sinus rhythm becomes an extremely difficult if not impossible task Especially in patients with left sided connections where the atrial end of the bypass originates in an area which is activated late during sinus rhythm contribution to ventricular excita*tion can be very small* [14] *This as we have seen* [31] may lead to QRS complexes showing rS complex*es in Leads* V_3R V_1 *and* V_2 *which according* to Rosenbaum and co workers [32] classification, would be called Type B (right sided) Wolff Parkinson White[1]

It is in our opinion therefore essential to bring out the maximal contribution to ventricular activation over the accessory pathway by giving the earliest atrial premature beat during atrial pacing which is conducted over the accessory pathway to the ventricle before one can start a study on the relation between QRS configuration and the site of ventricular insertion of the bypass in the Wolff Parkinson White syndrome Even then, we still have the problem that at present, we are not informed about the size of the area in different sites of the ventricle where impulse formation results in identical QRS complexes in the 12 lead electrocardiogram The difficulties listed above are well illustrated in our four patients The electrocardiograms of patients

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Case reports

Ventricular parasystole and re-entry Clinical-electrophysiological correlations

Donald H Singer M D*
R Parameswaran M R C P E**
Frank T Drake M D
Sheridan N Meyers M D
Arthur A DeBoer M D
With the technical assistance of Allen Krissberg
Chicago Illinois

Clinicians and electrophysiologists have been intrigued with parasystole for many years because of the uncertainties concerning the electrophysiologic basis of protection (entrance block)[1,2] and the interrelationship between this and other types of ectopic ventricular rhythms[3] This report describes a patient with ectopic ventricular beats of both the parasystolic and re entrant variety whose electrocardiograms (ECG) provided strong suggestive evidence of re entrant excitation within or in the immediate vicinity of the parasystolic focus Ambulatory ECG monitoring by the Holter technique[4] afforded an opportunity to observe the characteristics of the arrhythmia over prolonged periods of time Correlations with data from microelectrode studies on isolated canine Purkinje fibers[5] and specimens of human heart muscle obtained from patients with heart disease[6,7] permit speculations concerning the electrophysiologic basis of protection and the possible interrelationships between parasystole and re entry

From the Reingold ECG Center and the Departments of Medicine and Pharmacology and Surgery Northwestern University Medical School, Chicago Ill.

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Reprint requests to Donald H. Singer M D Northwestern University Medical School, 303 E. Chicago Ave Chicago Ill. 60611

*Studies were carried out during Dr Singer's tenure as an Established Investigator of the American Heart Association (67 155)

**Dr Parameswaran current address is Albert Einstein Medical Center Philadelphia Pa.

Case report

A 23 year-old white woman, admitted for treatment of septic abortion, was noted to have frequent premature beats She had first become aware of palpitations six months to one year prior to admission but had had no other cardiac symptoms Physical examination revealed frequent premature beats a slight left ventricular lift and an intermittent third heart sound. Borderline cardiomegaly was noted on x ray of the chest. A standard 12 lead ECG was normal except for variably coupled premature beats and fusion beats (Fig 1) On a subsequent hospitalization right heart catheterization performed as part of the diagnostic evaluation, revealed normal pressures and a normal cardiac output His bundle electrograms[8] were recorded at the time of cardiac catheterization and confirmed the ventricular origin of the premature beats (Fig 2)

In order to assess the frequency of the premature beats and the need, if any for antiarrhythmic therapy the patient was electrocardiographically monitored on an ambulatory basis using the Holter monitor Since frequent premature beats as well as runs of ventricular tachycardia occurred throughout the day and night, antiarrhythmic therapy was instituted Intermittent ECG monitoring has been continued on an outpatient basis in order to observe changes in the characteristics of the arrhythmia and the response to drug therapy To date the patient has been observed for 20 months during which time she has been monitored for a total of 260 hours

Description of electrocardiographic records Figs. 3 to 7 show representative monitoring records (modified Lead II) obtained prior to institution of drug therapy Records in Fig 3 show the ventricular premature beats with variable coupling and a common interectopic interval periods of sustained ventricular rhythm and fusion beats suggestive of parasystole It can be seen that the long interectopic intervals, i e intervals between ectopic (parasystolic) beats separated by sinus beats, are precise multiples of the short interectopic (basic parasystolic) cycles and that the latter differ in duration by only 0 01 second. Actually the duration of the basic parasystolic cycle remained remarkably constant

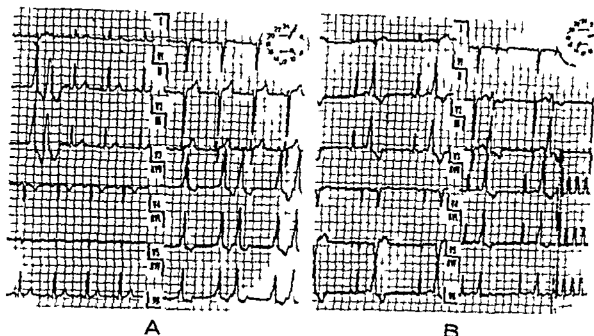


Fig 1 Panels *A* and *B* show two standard 12 lead ECG s obtained within several days of each other on an ECG machine *which records three leads simultaneously* Note the presence of both variably and fixed coupled ventricular ectopic beats and the similarity in configuration of these two types of beats in all leads (See text for discussion)

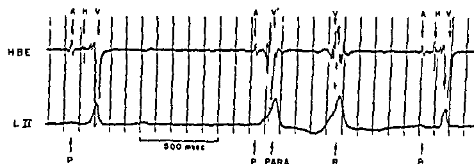


Fig 2 Simultaneously recorded Lead II ECG and His bundle electrogram (*HBE*) during sinus rhythm (beats 1 and 4) and during inscription of parasystolic and re entrant ventricular ectopic beats (beats 2 and 3 respec *tively)* Sinus P waves (*P*) *parasystolic* (*PARA*) and re entrant (R) beats are labelled on the surface lead. Atrial His and ventricular complexes of the intracardiac electrograms of sinus beats are designated *A H*, and *V* respectively *Ventricular complexes of ectopic beats are designated V' Note absence of H deflections preceding* the ectopic beats (See text for discussion)

throughout the 20 month monitoring period ranging be *tween 0 75 and 0 92 second*

The parasystolic beats frequently occurred in groups of two to five or six beats in succession the groups being separated by variable numbers of sinus beats (Figs 3 5 and 7) The groups appeared to be of two general types In the first type the component beats were regularly spaced and the longest and shortest interectopic intervals were precise multiples of each other (Fig 3) In groups of the second type the second parasystolic cycle i e interval between first and second *parasystolic* beats in the sequence was longer than the first parasystolic cycle In addition the first beat of such se quences often exhibited fixed coupling In the examples shown in Figs 4 5 and 7*A* the duration of the first cycle in such groups ranged between 0 81 and 0 90 seconds Prolonga tion of the second cycle was in the order of 0 16 to 0 30 sec onds Subsequent parasystolic cycles *if present generally* did not demonstrate further lengthening (Figs 4 5 and 7*A*) In *addition the longest and shortest interectopic intervals were* usually not precise multiples of each other (Figs 4 and 5) These characteristics which are atypical for parasystole will be commented upon subsequently

Fixed coupled ventricular premature beats were also com mon Most were coupled to preceding parasystolic and fusion beats (Figs 1 4 5 and 7*A*) *The fixed coupling suggested a* re entrant mechanism The close resemblance between *the* coupled beats and the parasystolic beats (both in the monitor lead (Figs 4 to 7) and in all 12 leads of the standard ECG (Fig 1) further suggested that re entry occurred within or in the immediate vicinity of the parasystolic focus It was also noted that the occurrence *of such* coupled premature beats often resulted in *shortening* (reset) of the subsequent parasystolic cycle *toward its basic length (Fig 4 Panel A* beats three and eight and Panel *B* beat seven Fig 5 beats e

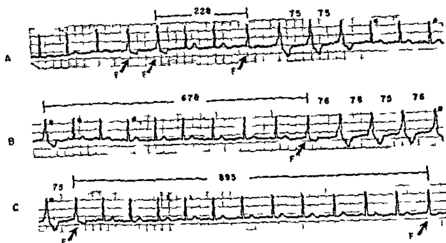


Fig 3 Panels *A*, *B*, and *C* show consecutive strips of a monitor lead The last four beats in *A* and the last beat in *B* are reproduced in succeeding strips Filled circles designate beats which are reproduced. The frequent ventricular ectopic beats exhibit typical characteristics of parasystole including variable coupling fusional complexes (arrows) and periods of sustained ventricular rhythm The interval between consecutive ectopic beats are virtually constant and the long interectopic intervals are almost precise multiples of the interval between consecutive ectopic beats Time intervals are expressed in hundredths of a second in this and all subsequent illustrations (See text for discussion.)

and *k*; Fig 7*A*, beat eight) Assuming that the parasystolic rate did not change abruptly this finding may be interpreted to indicate premature discharge of the focus by the re entrant impulse Since the parasystolic focus is presumed to be protected from impulses *originating at remote sites* premature discharge of the focus would have been feasible only if the re-entry had occurred within it An alternate explanation for the coupled beats namely that the short coupling" interval represented the actual cycle length of a rapidly discharging focus cannot be excluded. Lack of any demonstrable relationship between the coupling interval and the cycle length of the other parasystolic beats detracts from this possibility

Fixed coupling also occurred in relation to sinus beats (Fig 5 Fig 6 *B* to *D*) sometimes giving rise to long runs of bigeminy (Fig 6 *B* to *D*) The ventricular premature beats closely resembled the parasystolic beats in Figs. 3 to 6 suggesting a common site of origin. The fixed coupling of the premature beats again suggested re entrant mechanism the re entry occurring within or in the immediate vicinity of the parasystolic focus. Since the coupling was to the preceding sinus beat, re entry was presumably induced by the latter It will be noted that the coupling interval between sinus and re entrant beats in Figs 5 and 6 are closely comparable with each other but differ from intervals between parasystolic and re-entrant beats (Figs. 4 and 5) Such differences in coupling interval presumably reflect conduction differences in re entrant loops initiated by sinus and parasystolic beats.

The records in Fig 6 are of additional interest because of the frequent failure of parasystolic beats to appear when expected. It was previously noted that the duration of the basic parasystolic cycle ranged between 0 76 and 0 92 second. All of the sinus cycles in panel *A* as well as all *of the returning* cycles in panels B to *D* are considerably longer than the longest parasystolic cycles. Despite this no parasystolic beats appeared in records in panels *A* to *C*. In panel *D* the returning cycles are terminated by parasystolic beats following pauses of 1 20 to 1 24 seconds The first such beat is followed by a pause of 1 38 seconds in duration which is terminated by a sinus beat The duration of the pauses bears no demonstrable relationship to the duration of the basic parasystolic cycle This is atypical for parasystole the beats in question exhibiting more of the characteristics of ventricular escape beats than of parasystolic beats. Possible causes *for such irregularities* in timing of parasystolic events will be considered below

Although re entrant beats usually occurred as *isolated* events brief runs of re entrant ventricular tachycardia were also common particularly *during exercise* The incidence of isolated re entrant beats also increased during exertion (Fig 7 *B* to *D*)

Interpretation of records The postulated occurrence of re entry in or about the parasystolic focus would both intuitively and on the basis of findings from electrophysiological studies on human heart muscle (see Discussion) appear to provide a reasonable explanation for many of the peculiarities in rhythm exhibited by this patient The possibility that shortening of the parasystolic cycle following occurrence of *re entrant* beats resulted from premature discharge and "reset" of the parasystolic focus (Figs. 4 5 *and 7A*) has already been alluded to If it is assumed that re-entry within the focus could be concealed, i e the re-entrant impulse discharges the parasystolic pacemaker but decrements prior to emerging from the focus the lengthening of the second and subsequent parasystolic cycles seen in Figs 4 and 5 could be explained (see conduction diagram Figs 4 and 5) Fig 5 is of particular interest in this *regard. Beats a, b* and *c* are the first three beats of a parasystolic sequence The first parasystolic cycle (*a b*) is 0 82 second long The second parasystolic cycle (b-c) is 0 30 second longer than the first.

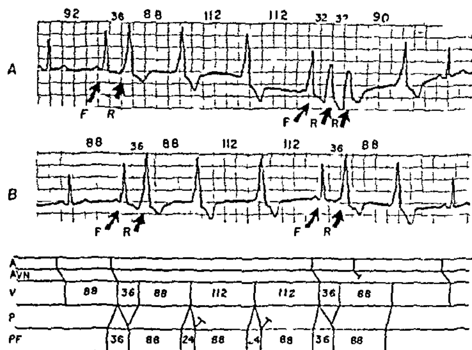


Fig 4 Nonconsecutive monitor records to show a typical parasystolic rhythm Panels A and B show two four beat parasystolic sequences which are initiated by a premature beat (R) and which consist of parasystolic and fusion (F) beats The basic (first) parasystolic cycle in each sequence is 0 88 seconds long The second and third parasystolic cycles are 0 24 seconds longer than the first. The premature beats appear to reset the parasystolic cycle back toward its basic length. Similiar coupling of premature beat to preceding parasystolic or fusion beats suggests a re entrant origin Close resemblance between premature and parasystolic beats further suggests that re entry occurred within or in the immediate vicinity of the parasystolic focus Large and small numbers above each panel indicate duration of parasystolic cycles and of coupling interval respectively The conduction diagram refers to records in panel B and illustrates postulated mechanisms underlying irregularity of parasystolic rhythm Activity in the atrium (A) A V node (AVN) and ventricle (V) is represented by the correspondingly marked horizontal panels. PF represents activity in the parasystolic focus The zone of protection (P) is shown as a region between the PF and V Vertical lines in PF indicate spontaneous and re entrant discharge of the focus Conduction times in P including time taken for re entrant discharge (oblique lines in P) are approximate estimates Reset of parasystolic cycle following coupled beat is explained in terms of premature discharge of focus lengthening of second and subsequent parasystolic cycles in terms of concealed re entry within focus. Differences in coupling intervals between manifest and concealed re entrant impulses presumably reflect differences in conduction velocity and/or path of impulse spread (See text for discussion)

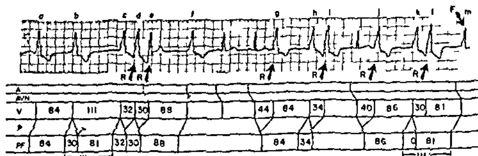


Fig 5 Monitor strip (top panel) showing atypical parasystolic rhythm together with conduction diagram (bottom panel) showing parasystolic and coupling intervals and postulated mechanism underlying irregularity of the parasystolic rhythm Conventions and symbols in diagram are the same as those in Fig 4 Re entrant beats (R) are coupled both to parasystolic and fusion (F) beats (coupled beats d, e i, and l) and to sinus beats (coupled beats g and j) Beat e appears to represent a fusional complex between a sinus and re entrant beat Beats a b and c are the first three beats of a typical parasystolic sequence The second parasystolic cycle (b to c) is 0 29 seconds longer than the first (a to b) The degree of prolongation closely approximates the duration of coupling intervals between parasystolic and re entrant beats (0 30 and 0 34 seconds) If it is assumed that the coupling intervals of manifest and concealed re entrant beats approximate each other then the prolongation of cycle b to c is explicable in terms of the occurrence of concealed re entry Note that the interval between parasystolic beats k and m, with its contained re entrant beat l, is the same as the interval b to c (See text for discussion)

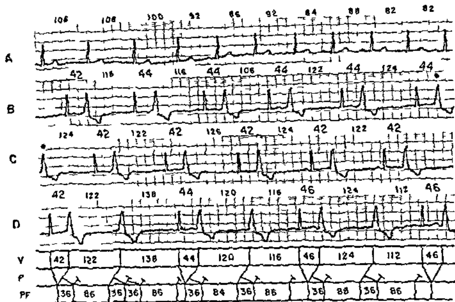


Fig 6 Representative monitoring records to show ventricular bigeminy the ventricular premature systoles exhibiting fixed coupling to the preceding sinus beat (panels *A* through *D*) Numbers above panels indicate duration of coupling intervals of premature beats (large numbers) and of sinus and returning cycles (small numbers) Panel *A* shows spontaneous variations in sinus rate present at time records in this figure obtained. Panels *B* through *D* which comprise a continuous strip show a period of sustained bigeminy Filled circles denote complexes reproduced in succeeding strip In panel *D* the returning cycles are terminated by parasystolic beats exhibiting characteristics of ventricular escapes. Similar configuration of coupled (re entrant) and parasystolic beat again suggest common site of origin. Note that most sinus and returning cycles are longer than the longest parasystolic cycle that is greater than 0 92 seconds The failure of parasystolic beats to appear when anticipated is explicable in terms of the effects of repetitive concealed re-entry as indicated by schematic conduction diagram (bottom panel) Symbols similar to those in Figs 4 and 5 (See text for discussion.)

The increment in cycle length is approximately equivalent to the coupling interval of re entrant beats (*d*, *i*, *l*) coupled to preceding parasystolic beats. If one assumes that the times required for concealed and manifest re entry approximate each other then the increment in cycle *b*-*c* is readily explained in terms of the occurrence of a single concealed re entry following parasystolic beat *b* Findings that the interval between parasystolic beats *k* and *m*, with its contained re-entrant beat *l*, is identical to that between beats b and c support this interpretation. Concealed discharge of the parasystolic pacemaker could also account for the absence of a numerical relationship between the long and the short interectopic intervals. The intermittent failure of the parasystolic beats to appear when anticipated (Fig 6) can also be explained in terms of the effect of concealed re entry if one invokes the concept of repetitive concealment.[9] The conduction diagram in Fig 6 provides a schematic representation of this explanation Additional factors, e g depressive effect of re-entrant impulses on subsequent impulse formation and on conduction within the focus or intermittent exit block may also have been involved.

Occurrence of re-entry within the focus would also provide an explanation for the occurrence of fixed coupling in parasystole Other explanations which have been previously invoked[10] to explain this phenomenon, and which presume that the fixed coupled beats are parasystolic rather than re entrant, would appear to be less applicable to the record shown in Fig 6 More specifically the variability in sinus rate (Fig 6) and the absence of any demonstrable relationships between the sinus and parasystolic rates make it unlikely that the fixed coupling resulted from a fortuitous numerical relationship between these variables The variability in sinus rate also makes it unlikely that fixed coupling resulted from regular discharge of the sinus by parasystolic impulses particularly in the absence of discrete evidence for retrograde atrial activation A third possible explanation for this phenomenon, namely that the parasystolic beats can only emerge from the focus during a "supernormal phase of conduction induced by the preceding sinus beats would also seem inapplicable in light of records in panel *D* of Fig 6 showing appearance of the former independent of prior sinus activity

Discussion

The complex ventricular arrhythmia described in this report would appear to be best explained in terms of the occurrence of manifest and concealed re entry within or in the immediate vicinity of a parasystolic focus.

Occurrence of re entrant excitation in parasystolic foci would have major implications with respect to current concepts concerning

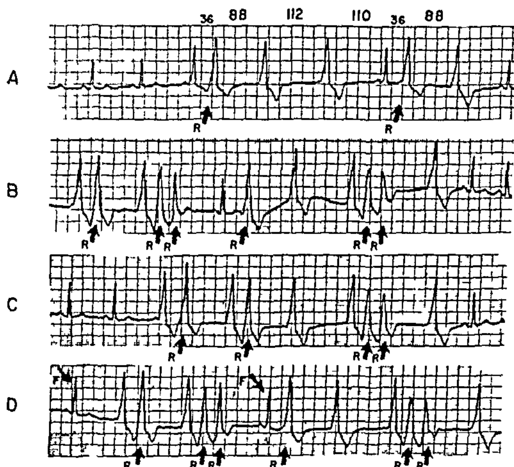


Fig 7 Representative records to show changes in parasystolic and re entrant type beats with exertion Panel *A* shows pre exercise record Large and small numbers above panel show duration of parasystolic cycles and of coupling interval respectively Panels *B* through *D* show changes with exertion (fast walking) Note increase in numbers of re entrant beats and appearance of brief runs of ventricular tachycardia Parasystolic rate has changed only minimally

parasystole For reasons to be cited subsequently, re entrant activity could theoretically result in marked irregularities in the timing of parasystolic foci Since the ECG diagnosis of parasystole is based on an analysis of the timing of ectopic beats, peculiarities in timing of parasystolic events resulting from re entrant ex citation would accentuate difficulties in the diag nosis of this disturbance Conversely, it would also provide a reasonable explanation for many of the irregularities of parasystolic rhythms which are otherwise difficult to explain As noted previously, many of the peculiarities in rhythm observed in the patient under discussion would seem to be best explained in these terms The oc currence of re entry in parasystolic foci also poses questions about the nature of parasystolic ventricular tachycardia It seems reasonable to suppose that at least some instances of ventricu lar tachycardia, including the brief bursts which occurred in the case under discussion (Fig 7), may be re entrant From a clinical viewpoint, the occurrence of re entry in parasystolic foci might, therefore, be expected to make the prognosis more guarded

An understanding of the genesis of re entry within parasystolic foci, as well as the interrela tionships between parasystole and other types of ectopic ventricular rhythms would be greatly facilitated by an understanding of the elec trophysiological basis of parasystole including the characteristic entrance (protection) and exit block The mechanisms that underlie entrance and exit block are controversial Scherf and asso ciates [2,11] on the basis of studies suggesting that parasystolic foci have a rapid rate of discharge explain "protection" in terms of rate related refractoriness Other investigators[1] suggest that parasystolic foci may also exhibit low firing rates. In such instances alternate mechanisms of "pro tection must be postulated. One widely held view[1,12] visualizes a zone of unidirectional block of uncertain cause surrounding the parasystolic focus Neither of these theories attempts to ex

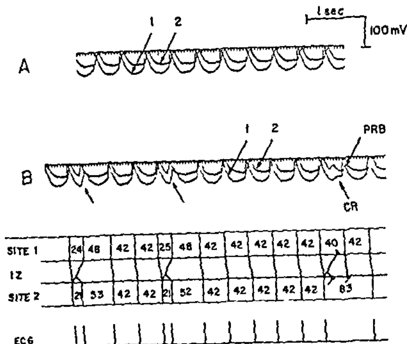


Fig 8. Simultaneously recorded transmembrane potentials from two adjacent spontaneously beating cells (*1* and *2*) in specimen of diseased human right atrial appendage Time and voltage calibrations are shown in upper right hand corner Panel *A* shows 1 1 propagation between the two sites, activity in cell 1 preceding that in cell 2 Note marked conduction delay between the two sites. Panel *B* shows three premature responses (beats 3 7 and 14 indicated by arrows below panel) Note reversed sequence of activation of the two recording sites, suggestive of a re-entrant type of mechanism The third premature response (*CR*) is decremented and does not disturb the basic rhythm However it acts to depress conductivity within the focus as evidenced by failure of the postre entrant beat (*PRB*) to propagate to cell 2 (concealed re entry) The conduction diagram (bottom panel) refers to record in panel *B* and illustrates how occurrence of manifest and concealed re-entry within automatic foci could result in an irregular rhythm Activity at sites 1 and 2 is represented by correspondingly designated horizontal panels. Numbers indicate intervals between site 1 and site 2 beats respectively in hundredths of a second. *IZ* designates intervening zone of conduction delay in which re-entry occurs Panel designated "*ECG*" shows irregular rhythm which could result at a remote recording site (Modified after Singer D H Ten Eick R E Drake F., and DeBoer A Possible electrophysiologic model for parasystole in preparation)

plain the variability of entrance and exit block or the occurrence of re entry within parasystolic foci. The demonstrated interrelationship between automaticity and conduction [6] i e that the cyclical reduction in diastolic membrane potential which occurs in automatic cells as a result of spontaneous Phase 4 (diastolic) depolarization can cause alterations in conduction ranging from simple slowing to decrement and varying degrees of uni and bi directional block may be important in this regard. If a parasystolic focus is regarded as a collection of automatic cells undergoing diastolic depolarization at varying rates, these interrelationships provide a reasonable explanation for many of the peculiarities of parasystole Reduced levels of diastolic potential in the focus could underlie the entrance (protection) and exit block with changes in the degree and direction of block occurring in conjunction with spontaneous changes in the rate and extent of diastolic depolarization of the component cells. Changes in block due to this cause could explain alterations in the frequency with which parasystolic beats propagate to the remainder of the heart, that is, in the manifest parasystolic rate Sufficient depolarization could prevent propagation of the parasystolic impulse altogether with consequent disappearance of the ectopic beats Conversely increases in diastolic potential resulting from reduction in the extent of depolarization would decrease the degree of block The precise effects of such a change would, however be more difficult to predict. If the increase in diastolic potential results in diminution of exit block it would facilitate reappearance of parasystolic beats If on the other hand,

entrance block were diminished, it could result in the discharge of the parasystolic focus by the *sinus impulse*, causing disappearance of ectopic *beats* During periods of sinus slowing, impulses from the parasystolic focus could reappear in the form of ventricular escape beats (Fig 6, *D*), or runs of slow idioventricular rhythm (Figs 4 and 7)

Studies on the interrelationship between automaticity and conduction have also shown that *reduction in diastolic* potential due to spontaneous depolarization can result in re entrant excitation Findings of numerous coupled re entrant type beats in "protected" automatic foci in specimens of human heart muscle[6,7] provide further evidence in this regard. Examples of such beats in a focus located in a spontaneously beating specimen of human right atrium are shown in Fig 8 Similar findings have been made in specimens of ventricular epicardium from patients undergoing aneurysm resection[13,15] The role of diastolic depolarization in the genesis of re entrant activity within such foci was underscored by observations that abolition of the former resulted in the disappearance of re entry Conversely, recurrence of diastolic depolarization was accompanied by the reappearance of re entry

Re entry thus could also provide an explanation *for the occurrence of coupled rhythms in* patients with parasystole Since re entry within the focus can be induced both by parasystolic and sinus impulses, the re entrant beats could be coupled either to preceding parasystolic (Figs 4 and 5) or sinus beats (Figs 5 and 6) The appearance and disappearance of coupled beats in cases of parasystole would be facilitated by changes in conduction resulting from changes in diastolic potential Spontaneous changes in the characteristics of the ventricular arrhythmia from a typical parasystolic pattern to a fixed bigeminal pattern[3,16] (Fig 6) can be explained in similar terms if one postulates changes in diastolic potential which would permit the sinus impulse to both discharge the parasystolic focus and initiate re entry

The occurrence *of re entrant type* activity in 'protected automatic foci in isolated specimens of diseased human heart muscle commonly resulted in variable changes *in timing of* subsequent beats This was true both for concealed re entry (i e, re entry resulting in an impulse which decremented completely before it could emerge from the focus) and for manifest re entry (re entry resulting in a propagated beat) Changes in timing were due to a combination of factors particularly concealed discharge of the pacemaker by the re entrant impulse and accentuated depression *of conduction* within the focus following *re entrant impulses Alterations in subsequent* impulse formation were also a factor Depressive effects on conduction were generally manifested by the development of increased degrees of exit block (Fig 8) Although the example in Fig 8 shows the development of exit block for only a single beat following the occurrence of re entry, block commonly persisted for many beats.[6,7] Accentuation of block was particularly pronounced following concealed re entry To the extent that the protected automatic foci in human heart *muscle represent a model for parasystole,* these findings support the hypothesis that changes in impulse formation and conduction resulting from occurrence of manifest and concealed re entry could represent a major factor underlying irregularities in timing of parasystolic rhythms.

Many of the peculiarities in rhythm noted in this report would, in fact, appear to be most reasonably explained in just such terms The possibility that shortening of the parasystolic cycle following re entrant type beats (Figs 4 and 5) *may have resulted from* premature discharge of the focus by the latter has already been alluded to Changes in impulse formation and conduction resulting *from concealed re entry within* the focus, more specifically, concealed discharge of the parasystolic pacemaker, accentuated depression of conduction and increase in exit block, and depressant effects on subsequent impulse formation, are sufficient to explain such puzzling phenomena as the unexpected lengthening of the second parasystolic cycle and intermittent absence of a demonstrable numerical relationship between the longest and shortest parasystolic cycles They also provide an additional explanation for failure of the parasystolic beats to appear when anticipated (Figs 4 and 6)

Coupled premature beats isolated ventricular escape beats idioventricular escape rhythms, and parasystole are all known to occur in both the normal and diseased heart *On the basis of* the *electrophysiological* observations described above it seems reasonable to suggest that en*hancement of* automaticity in the His Purkinje

system may give rise to any of these types of dis turbances The specific nature of the arrhythmia in a given instance would be dependent on a number of variables including the location and geometry of the involved fibers, maximum levels of diastolic membrane potential and the rate and degree of diastolic depolarization Changes from one type of rhythm to another might thus result from changes in the diastolic potential within the cells of automatic focus This would afford one explanation for the variability in the characteristics of certain ventricular rhythms such as in the patient reported here

Summary

A 23 year old patient with ventricular parasystole is described. Detailed analysis of ECG s obtained during 260 hours of Holter monitoring revealed a complex arrhythmia best explained in terms of the occurrence of manifest and concealed re entry within the parasystolic focus. Re entry when manifest, resulted in pre mature beats coupled to the parasystolic beats and brief runs of ventricular tachycardia When concealed, re entry produced an irregularity in the timing of the parasystolic beats Re entry within the parasystolic focus was also induced by sinus beats, giving rise to a pattern of bigeminy Correlation with data obtained from glass microelectrode studies on canine Purkinje fibers and human cardiac tissue permits speculation regarding the electrophysiologic basis of protec tion and the possible interrelationships be tween parasystole and other types of ectopic ventricular rhythm

The authors wish to express their appreciation to Drs Borys Surawicz and Robert E. Ten Eick and to Mr Thomas Steffens for their constructive comments and criticisms.

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Cardiac tamponade

Report of a case after insertion of transvenous endocardial electrode

George J Kalloor
Coventry England

Cardiac tamponade after insertion of a trans venous endocardial electrode is described. It was associated with signs of cardiac tamponade Prompt recognition and treatment resulted in complete cure

Perforation of the right ventricle during place ment of a transvenous endocardial electrode is not uncommon [2] Although hemopericardium is a recognized complication of left heart catheteri zation,[3] it is extremely rare following pacemaker electrode insertion [4] It rarely causes symptoms or signs due to tamponade, and perforation of the right ventricle is usually detected either by failure of pacing or at thoracotomy [5,6] When tam ponade has occurred it has been recognized late and may cause death [7]

In the patient to be described, this complica tion was recognized early and prompt treatment led to survival

Clinical history

A man, 78 years of age presented with a histo ry of an Adams Stokes attack and complete heart block with a ventricular rate of 20 per minute Following insertion of a Cambridge de mand temporary pacemaking system, his rhythm changed to atrial fibrillation, right bun dle branch block, and left hemiblock Operation for insertion of a permanent demand system was undertaken on May 3, 1973 (Vitatron Model MIP 41 RT implanted unit and Lucas unipolar en docardial catheter No 977 200 01) During at tempts at placement of the permanent catheter it was noted to enter the pericardial sac on three occasions before an electrically satisfactory posi tion was found at the apex of the right ventricle Immediately after completion of the operation the blood pressure became unrecordable the car diac impulse became impalpable, and the venous pressure was clinically raised. Pericardial aspira tion was then attempted unsuccessfully and thoracotomy was rapidly undertaken The pericardial sac contained 300 ml of blood and clots which were evacuated. There was an im mediate recovery of blood pressure Inspection of the right ventricle revealed two puncture holes at the apex which appeared to have sealed them selves spontaneously and were not sutured. The wounds were then closed with chest drainage Following this operation, the patient made an uninterrupted recovery and was discharged on the twelfth day, the pacemaker having been functioning satisfactorily throughout this time

From the Department of Cardiothoracic Surgery Walsgrave Hospital Coventry England
Received for publication Nov 12 1973
Reprint requests to Dr George J Kalloor Department of Cardio thoracic Surgery Walsgrave Hospital, Coventry England.

Discussion

Though a rare complication, cardiac tam ponade should be suspected following pacemaker insertion if the blood pressure becomes reduced and/or the venous pressure rises Fluoroscopy is helpful in showing poor pulsation and possible in crease in the size of the cardiac silhouette Pericardial aspiration does not appear to be helpful as a diagnostic aid since clots are common and often one cannot be certain as to the origin of the blood withdrawn The only effective treat ment is thoracotomy as exemplified by this case report.

I wish to express my sincere thanks to Dr J Pilcher and Mr W G Williams for allowing me to report this case and for their valuable help in preparing this paper

this group (31 per cent) had received antibiotic therapy prior to taking blood for culture

Sixteen (55 per cent) of the group had a fever of 100° F or greater on admission while 8 (27 per cent) experienced septic fluctuations during their hospital courses Sixty two per cent had a leukocytosis of greater than 12 000 per cubic millimeter a similar number demonstrated hemoglobin of less than 12 grams Splenomegaly and splinter hemorrhages were uncommon findings being detected in 17 per cent and 34 per cent of the instances respectively Roth s spots Osler s nodes and Janeway s lesions were not noted.

There were slight differences in clinical manifestations among patients suspected to have bacterial endocarditis and those detected postmortem (Fig 1) The presence of petechiae and splenomegaly was greater antemortem whereas neurologic signs and the degree of leukocytosis were more common in the group detected at autopsy The average splenic weight in the latter group was 286 grams Taken in context, these findings substantiate the similarity between these two groups and stress the importance of adequacy and thoroughness of physical examination

Strikingly 14 (48 per cent) of the total group received inappropriate antibiotic therapy and 21 (72 per cent) of the 29 patients in the older age group died. There was no significant correlation between duration of illness from onset of hospitalization until time of death or discharge and the degree of fever or leukocytosis The etiologic agent likewise was unrelated to the degree of pyrexia leukocytosis or morbidity Of six patients infected with coagulase positive staphylococcus three died within one to two weeks of hospitalization three within four to eight weeks Length of clinical course until death in patients with endocarditis caused by streptococcal viridans and alpha streptococci was similar

Specific anatomic correlations were not possible in all cases in this series However of the total number of cases examined postmortem 19 only a single instance of acute chordal rupture and four with acute cusp rupture (2 aortic 2 mitral) were recorded. There were two instances each of myocardial abscess, suppurative myocarditis, and left atrial extension of infective vegetation

Table I Presumed predisposing causes in 29 patients

Cause	*No cases*
Decubitus ulcer	4
Dental caries	4
Dental manipulation	1
Purulent conjunctivitis	1
Aplastic anemia	1
Operative procedure	
Repeated urethral catheterizations	1
Postoperative transurethral resection	2
Prostatic biopsy with perineal abscess	1
Infected Berry button	1
Herniorrhaphy	1
Ureteroileostomy with enterocutaneous fistula	1
Colectomy with ileocutaneous fistula	1
Gastric resection with wound abscess	1
Small bowel resection	1
Bleeding leg ulcer with tight urosheath and penile necrosis	1
Unknown	8

One patient appears in both categories

Table II Bacteriologic isolates in 29 cases

Organism	*No. cases*
Staphylococci	
Coagulase (+)	6
Coagulase (−)	1
Streptococci	
Viridans	7
Pyogenes	1
β Hemolytic	1
Enterococcus	3
D pneumoniae	1
E coli	1
Unknown	8

and single examples of mitral ring abscess and *aortic arch endarteritis* Occlusion of medium size blood vessels, predominantly intra abdominal was noted in 17 per cent of the cases

Discussion

In a recently reported series[1-8] the incidence of infective endocarditis in patients older than 60 years varies between 12 and 45 per cent. The present figure of 21 per cent is within this range Although the precise nature of underlying heart disease is uncertain in most of our cases postmortem examination confirmed a rheumatic

Infective endocarditis in patients over age 60

Mark M Applefeld M D*
Richard B Hornick M D
Baltimore Md.

Few diseases present greater insurmountable difficulties in diagnosis than infective endocarditis No less a student of the disease than William Osler stressed that fully one half of the patients are detected postmortem [17]

This diagnostic dilemma is particularly true in the older patient [1 4 12 15] Recent reviews[1 2 7 13] have not specifically stressed the problems of detection and management in patients over age 60 This paper will attempt to re emphasize pertinent aspects of infectious endocarditis in the elderly

Methods and materials

A retrospective analysis was made of the records of patients admitted to the University of Maryland Hospital between the years 1950 through 1970 with a diagnosis of bacterial endocarditis A search was also undertaken of autopsy reports of patients with similar diagnoses during the same period To be included for analysis, patients were required to manifest (1) positive blood cultures fever greater than 100° F splenomegaly or signs of peripheral embolization, heart murmur and hematuria, or (2) heart murmur, pyrexia over 100° F hematuria and/or splenomegaly with signs of peripheral embolization leukocytosis on admission greater than 12,000 per cubic millimeter and hemoglobin less than 12 grams, or (3) negative blood cultures fever greater than 100° F, heart murmur, hematuria splenomegaly and signs of embolization, or (4) a pathologically proved diagnosis of infective endocarditis One hundred and thirty six case records fulfilled the above criteria, 29 (21 per cent) patients, 60 years or older, will be discussed.

Results

Of the 29 patients 20 (85 per cent) were 65 years or older, 15 (51 per cent) were over 70 years of age Pyrexia of unknown etiology was the presenting complaint in 14 instances (48 per cent) Over one third of the patients[3] presented with neurologic signs, most commonly coma or hemiplegia of acute onset If disorientation is included, the figure is increased to 45 per cent. The danger of incriminating an infectious process as the sole cause of alteration of sensorium in this age group is recognized Despite neurologic changes only three patients received diagnostic lumbar puncture

The predisposing causes of illness include 10 (35 per cent) secondary to an operative procedure 9 (31 per cent) related to dental manipulation or decubitus ulcers and 8, cryptogenic (Table I) The vast majority of infections occurred in patients with known organic aortic valvular disease, primarily of a " rheumatic" etiology Eight patients (27 per cent) had aortic valvular insufficiency 8, aortic stenosis 2 (7 per cent), calcific aortic stenosis 10 (34 per cent) mitral regurgitation, and in 10 no murmur was detected New regurgitant murmurs were noted in 4 instances (14 per cent) aortic in 3 instances and mitral in 1 instance

Organisms of the staphylococcal or streptococcal group were the causative agents in 20 cases (69 per cent) (Table II) Endocarditis caused by fungae or rickettsiae was not noted Twenty one patients (72 per cent) had two or more positive blood cultures for the infecting agent while 9 of

From the Division of Infectious Diseases Department of Medicine University of Maryland School of Medicine Baltimore Md. 21201

Reprint requests should be addressed to Dr Hornick

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* Currently Fellow in Cardiology Georgetown University Hospital Washington D C

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There were slight differences in clinical manifestations among patients suspected to have bacterial endocarditis and those detected postmortem (Fig 1) The presence of petechiae and splenomegaly was greater antemortem whereas neurologic signs and the degree of leukocytosis were more common in the group detected at autopsy The average splenic weight in the latter group was 286 grams Taken in context these findings substantiate the similarity between these two groups and stress the importance of adequacy and thoroughness of physical examination

Strikingly 14 (48 per cent) of the total group received inappropriate antibiotic therapy and 21 (72 per cent) of the 29 patients in the older age group died. There was no significant correlation between duration of illness from onset of hospitalization until time of death or discharge and the degree of fever or leukocytosis The etiologic agent, likewise was unrelated to the degree of pyrexia leukocytosis or morbidity Of six patients infected with coagulase positive staphylococcus three died within one to two weeks of hospitalization three within four to eight weeks. Length of clinical course until death in patients with endocarditis caused by streptococcal viridans and alpha streptococci was similar

Specific anatomic correlations were not possible in all cases in this series. However, of the total number of cases examined postmortem 19 only a single instance of acute chordal rupture and four with acute cusp rupture (2 aortic 2 mitral) were recorded. There were two instances each of myocardial abscess, suppurative myocarditis, and left atrial extension of infective vegetation and single examples of mitral ring abscess and aortic arch endarteritis Occlusion of medium size blood vessels predominantly intra abdominal was noted in 17 per cent of the cases

Table I Presumed predisposing causes in 29 patients

Cause	*No cases*
Decubitus ulcer	4
Dental caries	4
Dental manipulation	1
Purulent conjunctivitis	1
Aplastic anemia	1
Operative procedure	
Repeated urethral catheterizations	1
Postoperative transurethral resection	2
Prostatic biopsy with perineal abscess	1
Infected Berry button	1
Herniorrhaphy	1
Ureteroileostomy with enterocutaneous fistula	1
Colectomy with ileocutaneous fistula	1
Gastric resection with wound abscess	1
Small bowel resection	1
Bleeding leg ulcer with tight urosheath and penile necrosis	1
Unknown	8

One patient appears in both categories

Table II Bacteriologic isolates in 29 cases

Organism	*No. cases*
Staphylococci	
Coagulase (+)	6
Coagulase (−)	1
Streptococci	
Viridans	7
Pyogenes	1
β Hemolytic	1
Enterococcus	3
D pneumoniae	1
E. coli	1
Unknown	8

Discussion

In a recently reported series [1-8] the incidence of infective endocarditis in patients older than 60 years varies between 12 and 45 per cent. The present figure of 21 per cent is within this range Although the precise nature of underlying heart disease is uncertain in most of our cases postmortem examination confirmed a rheumatic

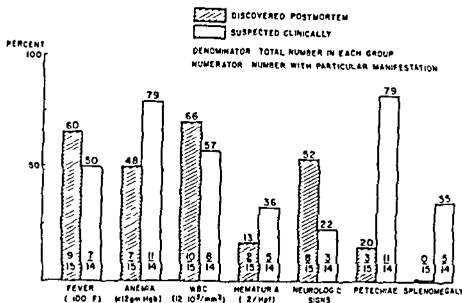


Fig 1 Findings detected antemortem and at necropsy

etiology in 4 (14 per cent) and calcific aortic stenosis in 2 (7 per cent) No organic valvular lesion was noted in 14 (48 per cent) cases Robinson [16] in a study of pathologic specimens reported an incidence of rheumatic heart disease in 31 per cent and calcific aortic stenosis in 10 per cent the remainder occurred in apparently normal hearts Roberts and Buchbinder[23] noted anatomically normal valves in 53 per cent of their patients This contrasts with Lerner and Weinstein s series[1] in which 50 per cent of the vegetations in bacterial endocarditis involving this age group occurred on rheumatic valves 30 per cent on normal valves These figures reemphasize the spectrum of this disease and its propensity to affect undamaged cardiac valves

A relative minority (30 per cent) of the infecting agents were of low virulence the remainder, either unidentified or pathogenic bacteria such as coagulase positive staphylococci enterococcus *Diplococcus pneumoniae* and *Escherichia coli* (Table II) In other studies [4,7] isolation of usually low virulence organisms occurs with similar frequency The role of antecedent staphylococcal infections has also been noted previously [1,9] Twenty seven per cent of our total number of cases of staphylococcal endocarditis appeared in the older age group in 71 per cent of these patients, underlying valvular heart disease was not previously known to exist In Wilson s and Hamburger s study[9] of patients surviving staphylococcal septicemia and presumed to have infective endocarditis 43 per cent apparently had no previous valvular heart disease In those who died, essentially the same figure pertains Thus the potential seriousness of staphylococcal bacteremia is again recognized and we concur with the current recommendation[1,9] of treatment with appropriate agents for a minimum of six weeks

Until 1972, there are only nine well documented cases of fungal endocarditis reported in the English literature in persons over 60 [18,22] The organisms identified were Candida, three cases *Histoplasma capsulatum*, two cases and single examples of *Blastomyces dermatitides*, Mucor, *Aspergillus fumagatum*, and *Torulopsis glabrata*. Clinical signs of endocarditis were detected premortem in two patients each caused by the genus Candida At necropsy valvular vegetations were noted in five instances the remaining lesions involved either the atrial and/or ventricular endocardium Only three patients over age 60 have been reported with endocarditis caused by *Rickettsia burneti* [24,25] Two patients survived their illness, one required aortic valve replacement To our knowledge none have been reported from the United States

The lack of a febrile response has been commented upon [1,10,17] In Jackson and Allison s series [10] although no figure is specifically mentioned pyrexia was noted on admission in 44 per cent but was consistently absent in 25 per cent of their patients In our study 55 per cent had fever of at least 100 5° F during their hospitalization 27 per cent demonstrated a septic type curve

during their illness However the number of patients remaining entirely afebrile re emphasizes the potentially occult nature of this disease Only three patients showed neither fever or leukocytosis negative findings stressed by Gleckler[26]

Twenty per cent of patients had either sterile blood cultures or no specimens taken If all of these are considered to be instances of abacteremia an unlikely assumption our figure approaches that of others[1 2 5 7] In fact this appears to be an overestimate and suggests that the majority of patients will indeed manifest bacteremia Seventy six per cent in our series showed two to ten positive cultures 50 per cent between two and four positive cultures This substantiates earlier work[11 23] Thus pyrexia leukocytosis, and positive blood cultures remain useful markers of the presence of this disease

Our incidence of splenomegaly 17 per cent probably spuriously low is strikingly less than that of others[1 5 10 12 14] while that of splinter hemorrhages 34 per cent is within the reported range[1 5 12 10] Osler s nodes Roth s spots and Janeway s lesions were not detected in this series Obviously the presence or absence of these physical signs is dependent upon the care with which they are sought Zemen and Slegal s admonition[15] it is obvious that when the possibility of endocarditis is unsuspected, little time will be given to looking for skin lesions (and splenomegaly) merits emphasis

Our mortality rate of 72 per cent simulates other data[2 4 7 10 12] The reasons for our large number of treatment failures are uncertain Illness was fulminant in some causing an early death However other instances represented patients in whom bacteriologic isolates were apparently known and yet therapy not instituted or inadequate dosage regimens used. The reasons were probably related to variation in clinical competence among the responsible *physicians* and in their more cautious attitude toward handling geriatric patients Of those patients treated appropriately 60 per cent survived

In conclusion this series demonstrates that infective endocarditis is not necessarily an uncommon disease with unusual manifestations in patients over age 60 In the appropriate clinical setting i e fever and/or leukocytosis with or without a cardiac murmur it needs to be carefully excluded. Dramatic clinical differences do not appear to be present between patients being treated appropriately and those who are not Blood cultures will yield the infecting agent in the majority of instances. Abacteremic cases do occur albeit infrequently Antibiotic regimens should be judiciously selected with treatment in proper dosage of adequate periods Only in this manner can the excessive mortality from this disease be decreased

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Review

Electrolyte and antiarrhythmic drug interaction

Leonard S Dreifus, M D
Irany M de Azevedo M D
Yoshio Watanabe M D
Philadelphia, Pa.

The precise action of antiarrhythmic agents still remains unclear[1] and even less is known of the interactions of antiarrhythmic drugs that are often exhibited in the wake of each other Furthermore there is still an incomplete understanding of the mechanisms engendering various cardiac arrhythmias despite the recent contributions by investigators using ultramicroelectrodes and His bundle techniques Too often the clinician surprised by the actions of a specific agent may be unable to predict whether the drug will be beneficial or precipitate more sinister problems Unfortunately the various antiarrhythmic agents available for clinical use have complex and competing mechanisms of action and it is impossible to produce the most therapeutic effects under all conditions These problems will begin to unfold as we discuss the pertinent information Since knowledge of the combined action of the various antiarrhythmic agents is so meager we will confine the scope of this review to those agents and electrolytes that are of clinical importance Indeed the clinician must gain enough information to utilize antiarrhythmic agents in combination while avoiding the pitfalls of antagonistic actions that may prove detrimental to the patient

From the electrophysiologic standpoint, the genesis of cardiac arrhythmias is often divided into three categories (1) disturbances of impulse formation (2) disturbances of conduction due to altered refractoriness or responsiveness and (3) combinations of (1) and (2) Many other mechanisms have been identified that may affect the onset or perpetuation of cardiac dysrhythmias and a more detailed discussion can be studied in other texts[1-12] The pathophysiology engendered by myocardial disease may result from ischemia inflammation electrolyte abnormalities mechanical injury or neurohumoral derangements the resulting cardiac dysrhythmia must be managed by restoring or controlling the ventricular rate by a sinus rhythm favorably manipulating the membrane characteristics of the diseased myocardial fibers for the dysrhythmias or substituting another rhythm or cardiac pacing

In any discussion of the observed membrane effects of antiarrhythmic agents one must recognize that changes in electrical activity are most probably related to their antiarrhythmic actions but sharp differences of results among various investigators only bring into focus the problems in experimental design species and electrolyte concentrations manifest in the studies Furthermore there is no general agreement that the observed membrane alterations constitute a clinically significant antiarrhythmic action Hoffman[13] and Hoffman and Bigger[14] have summarized the possible membrane effects of antiarrhythmic agents and have classified these compounds into two groups The quinidine like group includes quinidine propranolol procainamide and several less important agents[14] These agents decrease automaticity and responsiveness and prolong the refractory period. A second group of antiarrhythmic drugs includes diphenylhydantoin (DPH) lidocaine and, under certain conditions, the catecholamines. Lidocaine and DPH decrease automaticity and increase responsiveness and the refractory period. However this last group is far more heterogeneous with respect to

From the Department of Physiology and Biophysics and the Department of Medicine Hahnemann Medical College Philadelphia, Pa.
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Reprint r que ts to Leo rd S Dreifus M D 1320 Race St. Philadelphia, Pa. 19107

Table I Classification of antiarrhythmic agents

Group 1	*Group 2*	*Group 3*
Quinidine	Diphenylhydantoin	Bretylium tosylate
Procainamide	Lidocaine	
Propranolol		
Antazoline		
Ajmaline ester (MCAA)		
Disopyramide phosphate		

membrane action and several investigators have observed sharp differences in their action, particularly when the drug concentration and potassium concentrations have a wide range [14-36]

Bretylium tosylate, a beta blocking agent with potent antiarrhythmic action, cannot be included in these two groups and could possibly identify a third group[18,37] (Table I) The precise action and the prevailing controversy concerning this agent will be discussed later

Finally, the actual beneficial effects of antiarrhythmic agents may be observed only in depressed cardiac fibers There is a possibility that regions of depressed cardiac fibers are the actual sites of abnormal impulse formation and conduction causing arrhythmias, and these observations cannot be disregarded [1,18,19]

It is extremely interesting that all these agents including bretylium, favorably affect the change in the effective refractory period in accord with the duration of the action potential

The membrane actions that directly affect cardiac fibers will be described as a basis for the interaction of various electrolytes and antiarrhythmic agents

Automaticity

Automaticity is a special property of pacemaker cells found in the S A node and the intra atrial and AV conducting systems and refers to the ability of specialized cardiac cells to attain spontaneous diastolic Phase 4 depolarization [14] Thus any agent that decreases the rate of Phase 4 depolarization or displaces the resting potential away from the level of the threshold potential would be effective in suppressing arrhythmias secondary to enhanced automaticity Among agents having this specific effect on Purkinje fibers we find quinidine, procainamide, lidocaine diphenylhydantoin, some antihistaminic drugs, potassium, propranolol, and pronethalol [14,17,38] The magnitude of this change is related to concentration and it has been argued that this effect may be seen only in the presence of toxic concentrations [14] At extremely high concentrations quinidine and to a lesser extent, procainamide may increase automaticity by augmenting and altering the voltage time course of Phase 4 depolarization [5] Hence, the concomitant low concentrations of lidocaine and procainamide or propranolol may offer important advantages over a high concentration of a single agent. Combined therapy with diphenylhydantoin[28] or a Group 3 drug such as bretylium does not appear warranted to augment the depression of Phase 4 depolarization Furthermore, quinidine and procainamide decrease the effect of the vagus on cells of the sinus node, the atrium, and the AV node Propranolol interferes with the effect of the sympathetic efferent fibers on all parts of the heart Hence, the extent to which any automatic cell is slowed by one of these agents may depend on the complex balance of their direct and indirect actions [18]

Refractoriness

The effective refractory period (ERP) is measured by the ability of an early stimulus to evoke a propagated response (Fig 1) In the case of quinidine procainamide, and magnesium the action potential duration (APD) is prolonged by slowing of repolarization [14,17] However in the presence of propranolol diphenylhydantoin, lidocaine,[14] and possibly bretylium [14,37] the APD is reduced and hence the apparent effective refractory period is reduced However, the shortening of the effective refractory period is less marked than the shortening of the action potential duration This implies that whether APD is either increased or decreased, there is relatively greater shortening or less lengthening of the APD with respect to the effective refractory period and repolarization will have progressed farther in both instances This restricts the earliest possible response after a previous discharge to a higher membrane potential and consequently the premature action potentials have a greater rate of depolarization and a greater amplitude These factors increase the efficiency of the premature response as a stimulus to the surrounding tissue and permit a more rapid and uniform propaga

tion[118] Hence salvos of premature ventricular systoles or ventricular fibrillation are less likely to occur even though ectopic beating is not suppressed

From information based on these studies and more recent observations on bretylium tosylate[57] the combined use of antiarrhythmic agents may be additive or antagonistic In addition the clinician can select agents other than quinidine or procainamide that would not further prolong or abnormally increase the QTc interval On the other hand, he can select agents such as lidocaine bretylium or propranolol which tend to shorten the QTc interval The combined use of drugs in Group I with drugs in Group II or III may not have any apparent effect on the APD consequently inappropriate combinations of antiarrhythmic agents may offer little therapeutic effect while other combinations could be extremely effective in managing cardiac arrhythmias

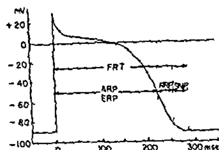


Fig 1 Action potential of typical ventricular fiber showing the relationship of refractory periods Effective refractory period *(ERP)* There is no response to a stimulus of any magnitude the cell is absolutely refractory *(ARP)* After approximately 220 msec the fiber can be re-excited by a suprathreshold stimulus during the relative refractory period *(RRP)* After approximately 260 msec a subthreshold stimulus can re-excite the fiber during the super normal period *(SNP)* and beyond this threshold stimuli can produce a second response Full recovery time embraces the entire period of systole *(FRT)* (From Hoffman B F and Cranefield, P F Electrophysiology of the heart New York, 1960 McGraw Hill Book Company Inc Reproduced by permission)

Responsiveness

It has been widely accepted that the rate of depolarization during phase zero of the action potential (dV/dt) is the main determinant of conduction velocity Furthermore it has been well established that, generally the higher the membrane potential at the beginning of phase zero depolarization the greater the dV/dt[31] This relation is illustrated in the membrane responsiveness curves In an agent causing an increase in the membrane resting potential (hyperpolarization) the rate of depolarization will be increased and the conduction velocity will accordingly be higher For example if the membrane potential is increased from −60 to −80 mv rightward along the center curve (solid line) the maximal rate of depolarization is markedly increased from 50 to 350 volts per second. Procainamide quinidine propranolol and practolol shift the curve to the right decreasing conduction velocity while DPH may shift the curve to the left, increasing conductive velocity (Fig 2) Hence a decrease in responsiveness may interrupt a re entrant rhythm by further decreasing conduction in the depressed pathway by converting a re entrant path from one with unidirectional to one with bidirectional block Drugs of Group 1 such as quinidine procainamide or propranolol may produce such effects. The other group of antiarrhythmic agents may improve responsiveness and could simply abolish unidirectional block

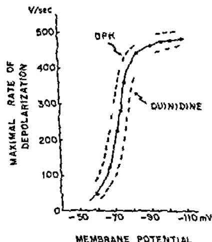


Fig 2 Schematic membrane responsiveness curves showing relation between the level of membrane potential and the maximal rate of depolarization. Solid line represents the normal broken line and chain line show the curves in the presence of diphenylhydantoin *(DPH)* and quinidine respectively (Reference 18 Fig 2)

Finally it should be stressed that the relation between membrane potential and responsiveness is similar whether reduction in membrane potential results from incomplete repolarization or Phase 4 depolarization For example if an action potential is initiated after Phase 4 depolariza

tion it has a reduced membrane potential and consequently a decreased rate of Phase 0 depolarization Such an action potential would propagate slowly or even decrement to the point of block

If there was a decrease in the slope of Phase 4 depolarization, the membrane resting potential would be greater and a better action potential might result despite the decreased responsiveness However if there were marked or continued Phase 4 activity, agents such as the Group 1 drugs might cause block around an automatic pacemaker or render the automatic focus ineffective Drugs in Group 2 or 3, such as diphenylhydantoin or bretylium, would have an opposite effect As an example, the addition of bretylium in the presence of quinidine will restore the maximal rate of depolarization [37] Thus the reduction in responsiveness usually engendered by quinidine is reversed

When these agents are used in combination, they may have inconsistent effects or may nullify one another [37,38]

Digitalis potassium, and other antiarrhythmic agents

Although the interrelation between digitalis and potassium salts is generally well known [39-46] less information is available concerning the interaction of antiarrhythmic agents such as quinidine, lidocaine, procainamide, diphenylhydantoin, and propranolol [15 18,19 46 64] Alterations produced by these antiarrhythmic drugs in the wake of changing potassium concentrations have electrophysiologic as well as clinical significance in the approach to antiarrhythmic therapy

Digitalis

It has been repeatedly demonstrated that digitalis inhibits the active transport of sodium and potassium across the cell [47 64] Furthermore, frequent clinical as well as electrophysiologic observations of the interrelation between the changes in potassium concentration and digitalis induced arrhythmias indicate that the potassium ion is more important than the sodium ion [46 56 57] In fact, relative intracellular versus extracellular potassium concentrations may be crucial in the genesis or termination of cardiac arrhythmias [46 58]

Extensive studies of the action of digitalis glycosides on the transmembrane potential of ventricular fibers are in general agreement that digitalis shortens the action potential duration [58-64] On the other hand, the effects on membrane action and resting potentials and the rate of depolarization have been less consistent [60 63] In general digitalis decreases the action and resting potentials, upstroke velocity, heart rate and action potential duration under certain electrophysiologic conditions but shows diversified actions in the presence of various digitalis and potassium concentrations This would imply that a preexisting low or high potassium concentration may mask the typical effects of digitalis

Potassium

On the other hand, the electrophysiologic effects of either low or high potassium concentration are not decisive with respect to the mechanisms of ventricular arrhythmias It has been reported that a low potassium concentration increases diastolic depolarization in Purkinje fibers [66] Digitalis arrhythmias due to ectopic pacemaker activity could be suppressed by high potassium concentration and enhanced by low potassium concentration However, a high extracellular potassium level definitely shortens the action potential duration, an action synergistic with that of digitalis [66 67] It should be noted that elevation of potassium concentration to 7 5 mg per liter in the presence of digitalis engenders a further reduction in all electrophysiologic parameters and actually accentuates digitalis effects [68] As these alterations are usually accompanied by a disappearance of digitalis induced arrhythmias, the antiarrhythmic effects of potassium should be related at least in part to other electrophysiologic properties of potassium. Hence, four possible combinations of events[65] have been considered (1) Low extracellular potassium concentration is synergistic with digitalis glycoside in enhancing ectopic pacemaker activity (2) However, it may mask some of the other effects of digitalis (3) The incidence of ventricular arrhythmias is most frequent in the presence of low potassium and digitalis (4) High extracellular potassium antagonizes digitalis induced ectopic pacemaker activity but enhances the decrease in action potential duration and conduction velocity [68] Hence it may be concluded that effective antiarrhythmic drug therapy in the presence of digitalis may require normaliza

Table II Changes in conduction time in isolated, perfused rabbit hearts caused by lanatoside C when potassium concentration was normal or high

K concentration (mM.)	*Rate of atrial stimulation (beats/min.)*	*Concentration duration index of lanatoside C (mg liter⁻¹ hr⁻¹)*	*Incidence of second degree A V block*		*Conduction time (msec)*			
					Control	*Lanatoside C*	*% change*	*P*†
Normal (4 5)	151.0 ± 6.36	1.52 ± 0.17	6/10	A	25.3 ± 3.64	31.8 ± 6.25	+25.7	>0.05
				N	34.2 ± 1.28	60.9 ± 4.33	+78.1	<0.01
				HP	36.7 ± 2.64	40.3 ± 3.07	+ 9.8	>0.1
				A V	96.2 ± 5.23	133.0 ± 2.58	+38.3	<0.01
High (7.5)	159.7 ± 6.29	1.95 ± 0.05	1/10	A	28.4 ± 2.64	40.5 ± 4.74	+42.6	<0.01
				N	34.5 ± 2.63	50.7 ± 4.54	+47.0	<0.01
				HP	34.0 ± 1.29	45.1 ± 2.92	+32.6	<0.01
				A V	96.9 ± 3.81	136.3 ± 6.68	+40.7	<0.01

Abbreviations A = intra atrial N = intranodal HP = His Purkinje A V = total atrioventricular conduction time
Mean of 10 hearts ± standard error These conduction times were measured during control period (Control) and immediately before the development of second degree A V block or at the termination of experiment (lanatoside C)
†Calculated by paired Student's t test.

tion of the potassium concentration Recent studies with antikaliuretic diuretics such as amiloride show that they prevent the onset of digitalis induced arrhythmias[69] and have definite antagonistic effects in the presence of *digitalis* glycosides[70] as far as membrane resting potential height of action potential action potential duration and maximal rate of Phase 0 depolarization are concerned Perhaps the best known effect of digitalis is on AV transmission (Table II)[71,72]

Prolongation of the effective refractory period in the A V junction is caused *partly by vagal action* and partly by a direct effect on the nodal fibers[15,16,63,71,72] Characteristically digitalis engenders a low amplitude and upstroke velocity of the action potentials from the N region of the AV node[72] The rate of rise of Phase 0 (dV/dt) in nodal His (NH) fibers also appears to be decreased. Hence a greater decrement and failure of propagation may result within the AV node[72] Furthermore part of the increase in the so called effective refractory period of the AV transmission system results from concealment of rapid atrial impulses, especially in the presence of atrial fibrillation and, to a lesser extent of atrial flutter into the AV junction[73] Hence in the presence of repetitive concealment, fewer supraventricular impulses will propagate to the ventricles. Partial penetration into and concealed re entry within the AV junction could also inhibit subsequent AV transmission[73]

It should also be pointed out that the effects of digitalis on the electrical properties of the heart are mediated indirectly through the autonomic nervous system Indirect effects of digitalis usually are thought to be confined largely to the atria the S A node and the AV node These areas are richly endowed with vagal nerve endings Studies of the effects of vagal activity on automaticity of the frog sinus venosus[74] show that a slowing of the rate or even arrest of the pacemaker is produced because of a progressive decrease in the rate of digitalis (Phase 4) depolarization and because of hyperpolarization of the pacemaker fibers Application of acetylcholine to the S A node of the rabbit[75] also results in decreased automaticity caused by the decreased slope of diastolic depolarization and increased levels of resting potential The amplitude of S A nodal action potentials may be decreased but their duration is not altered appreciably The threshold potential is essentially unchanged. Action potentials of ordinary mammalian atrial myocardium show a marked acceleration of repolarization

Corresponding to the decrease in the duration of the action potential there is a shortening of both the absolute and the total refractory periods The resting potential of atrial fibers is in

creased if the initial level is low This results in an increase in the rate of rise of the action potential this latter change may cause the enhancement of conduction sometimes seen after vagal stimulation or acetylcholine administration Fibers from the several portions of the AV junctional tissue vary considerably in their sensitivity to acetylcholine those at the atrionodal junction (AN region) and in the node proper (N region) are most sensitive while the fibers in the lower portion of the node and the His bundle are rather insensitive Action potentials from the AN and N regions tend to become smaller and rise more slowly Step like prepotentials are accentuated, if present initially, or develop if not present previously These changes mirror the additional slowing of impulse transmission through the AV junctional tissue, particularly that at the atrionodal margin

Relation between potassium and digitalis

Some discussion seems appropriate concerning the relation between potassium and digitalis Many clinical[76-80] and experimental studies offer conflicting results dealing with the interrelation between digitalis and potassium and their effects on AV conduction[81-84] Fisch and colleagues[78,79] suggested that potassium may improve AV conduction in the presence of incomplete digitalization but may aggravate AV block when toxic amounts of glycoside are present Earlier work from our laboratory demonstrated that cardiac glycosides and potassium primarily affect different portions of the AV conducting system[71,85] Table II (from subsequent experiments)[72] confirms the earlier studies and indicates that lanatoside C almost selectively depresses conduction across the AV node with little or no delay in intra atrial and His Purkinje transmission[71,72] In another series of experiments a high concentration of potassium was shown to slow intra atrial and subnodal conduction[85] Potassium in high concentrations appeared to provide protective action for intranodal conduction rather than to produce any deleterious effects[85] Similar effects of potassium were reported earlier by Paes de Carvalho and Langan[86] Hence elevation of potassium may counteract the depressant action of cardiac glycosides on intranodal transmission but could cause further delay above and below the AV node

The contrasting effects of cardiac glycosides and potassium on specific regions of the AV transmission can be explained by the following electrophysiologic findings the characteristically low amplitude and upstroke velocity of the action potentials from the N region of the AV node are further decreased by lanatoside C The rate of depolarization in NH fibers also appeared decreased Hence, greater decrement and failure of propagation may result within the AV node In contrast, high concentrations of potassium caused a significant increase in the action potential amplitude of the N and NH fibers[65] This effect is most likely responsible for the apparent protection of intranodal conduction by perfusion with a solution having a high concentration of potassium against the depressing action of lanatoside C (Table II)

On the other hand several investigators reported some decrease in the amplitude of the action potential and the rate of depolarization in Purkinje fibers caused by cardiac glycosides[87] These changes could lead to a slower conduction velocity in this type of tissue However prolongation of the His Purkinje conduction by lanatoside C was not significant in the presence of a normal concentration of potassium (Table II) Differing experimental conditions in reports written in our study may explain this discrepancy Nevertheless the depressant effect of the cardiac glycoside on His Purkinje conduction appears minor High concentrations of potassium also were shown to decrease the resting potential of Purkinje fibers[88] Prolongation of the His Purkinje conduction time with occasional subnodal block produced by high concentration of potassium (Table II) can be explained on this basis When a large amount of glycoside is administered in the presence of elevated concentrations of potassium a slightly depressant effect of glycoside on His Purkinje conduction may be superimposed on the more marked depression of conduction by potassium A significant prolongation of the His Purkinje conduction time by lanatoside C in the group with high concentration of potassium (Table II) probably resulted from this interaction Additive effects of lanatoside C and a high concentration of potassium on ventricular action potentials have also been reported earlier[63]

Regarding intra atrial conduction de Mello and Hoffman[89] reported that a high concentration of potassium caused loss of excitability in ordinary atrial muscle when action potentials were

still recorded from the sinus and AV nodes as well as other specialized fibers of the atria The selective sensitivity to potassium of the atrial specialized tissues and atrial muscle fibers resulted in sinoventricular conduction in the absence of electrocardiographic P waves More recently Sano and colleagues[90] showed that so called sinoatrial block caused by a high concentration of potassium was actually intra atrial block On the other hand, cardiac glycosides produced no change in the size and shape of atrial action potentials at a dose engendering a positive inotropic effect[76 91] The action potential amplitude was decreased only at toxic levels of strophanthin associated with decreased contractility Hence significant prolongation of intra atrial conduction time by lanatoside C seen only in the group with a high concentration of potassium (Table II) can be attributed to the effect of potassium alone Evidence that cardiac glycoside itself does not markedly depress intra atrial and His Purkinje conduction is also supplied in a second series of experiments a potassium induced prolongation of conduction time in these regions did not show a significant difference between hearts with and those without lanatoside C[72]

If intranodal conduction is severely depressed by toxic doses of cardiac glycoside the beneficial effect of elevated potassium concentration may be insufficient to restore 1 1 conduction across the crucial N region of the AV node Thus intranodal block may continue On the other hand if infusion of potassium in digitalis intoxication really causes an unusually rapid elevation of plasma potassium concentration[82] this would result in additional conduction delay and block within the atria or the His Purkinje system or in both In this regard, the observations of Fisch and colleagues[79 82] can be validated. Potassium may aggravate AV block in digitalis intoxicated patients but may improve conduction in patients receiving smaller amounts of glycoside

Since cardiac glycosides increase diastolic depolarization in His Purkinje fibers[90 92] and since the resultant loss of membrane potential could cause a decreased rate of Phase 0 depolarization and slower conduction velocity[93] suppression of automaticity by a high concentration of potassium may sometimes improve the His Purkinje conduction[94] However it has been pointed out that in the presence of severe con

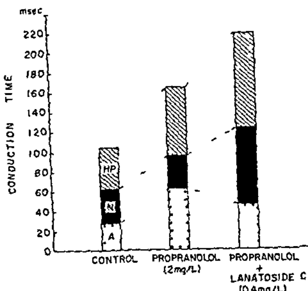


Fig 3 Site of A V conduction delay in the presence of propranolol and lanatoside C in isolated rabbit heart Intra atrial conduction *(A)* intranodal conduction *(N)* His Purkinje conduction *(HP)* Propranolol (2 0 mg/liter) increases the A and *HP* conduction time without discernible effect on intranodal conduction After administration of lanatoside C (0 4 mg /liter) the intranodal time is increased (Reference 18 Fig 8)

duction disturbance in the more proximal portion of the AV transmission system (e g the AV node) such suppression of His Purkinje automaticity may result in the abolition of subsidiary pacemakers and ventricular standstill This is another reason that great caution must be exercised in the administration of potassium in patients with AV block and possible digitalis excess.

Interrelation of propranolol hydrochloride and digitalis

The combined use of digitalis and propranolol probably represents one of the most significant advances in the control of supraventricular arrhythmias The complementary action of these agents slows the ventricular rate in the presence of atrial flutter and fibrillation Propranolol has been shown to depress both intra atrial and His Purkinje conduction while sparing intranodal conduction[18 9] This effect is similar to the effects of quinidine and a high concentration of potassium Furthermore in an in situ heart propranolol blocks the beta adrenergic receptors and, consequently indirectly enhances vagal or acetylcholine effect Hence intranodal conduction can also be depressed (Fig 3)

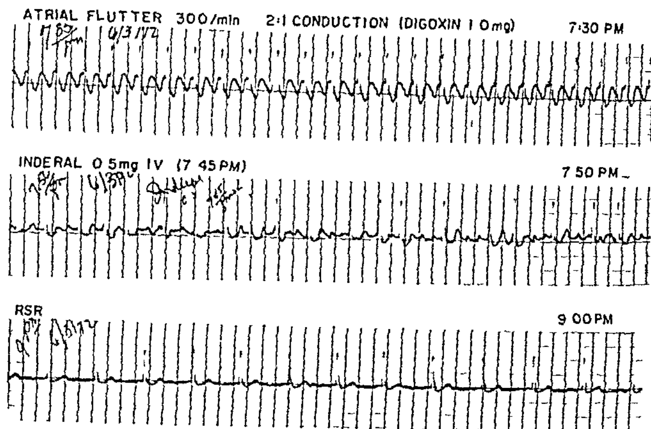


Fig 4 Combined effects of digoxin and propranolol *Upper strip* atrial flutter the ventricular rate was not slowed following 1 mg of intravenous digoxin (7 30 P.M) Following 0 5 mg of propranolol at 7 45 P.M there is a prompt slowing of the ventricular rate (7 50 P.M) and re establishment of sinus rhythm at 9 00 P.M The additive effects of both agents to slow the ventricular rate is rapid and effective

The additive effect of two different kinds of agents with depression of conduction in three portions of the AV transmission system, may be a possible mechanism in combination drug therapy It is imperative that a 'cholinergic dose' of digitalis be administered initially, usually 0 4 mg of deslanoside administered intravenously followed by 0 5 to 1 mg of propranolol administered intravenously 20 minutes later Thereafter each drug can be administered alternately in these increments every 30 to 60 minutes until the ventricular rate is controlled or sinus rhythm is reestablished (Fig 4) In short digitalis acting alone or enhancing acetylcholine effects will engender decremental conduction and slow AV transmission A large dose of propranolol will produce AV block The additive effects of beta blocking agents are interesting and appear extremely useful in slowing ventricular rate or terminating the mechanism in the presence of supraventricular dysrhythmias [18]

Interaction of potassium and quinidine

Interrelationship of quinidine and antiarrhythmic agents It has long been known that quinidine decreases the slow diastolic depolarization of Purkinje fibers and prolongs the effective refractory period.[63,96] Contrariwise the significant decrease in conduction velocity due to this drug may first appear as an antiarrhythmic effect but it has been postulated that marked slowing of conduction velocity throughout the ventricle could sustain re excitation and continue the arrhythmia The main actions of quinidine are characterized by a prolongation of the effective refractory period[15,63,80,81,96-101] and a marked decrease in the rate of depolarization [63]

However, the most significant reports concerning the interrelation of potassium and quinidine reveal that the decrease in the maximal rate of depolarization after the administration of quinidine is partially reversed by subsequent lowering of the potassium concentration In addition initial low potassium perfusion appears to block the expected effects of quinidine on ventricular fibers except for an increase in the action potential duration per unit of time [15,63] These effects were accompanied by higher action and resting potentials These antagonistic effects were also noted when other antiarrhythmic agents, such as antazoline, an antihistamine and

a local anesthetic type agent and SU 11636 were concurrently perfused with a low potassium concentration of 1 5 mEq per liter[15] On the other hand, when potassium concentration is elevated to 12 mEq per liter in the presence of quinidine there was a decrease in the maximal rate of depolarization height of action and membrane resting potentials Hence high extracellular potassium is generally additive with quinidine These additive effects may encourage the development of serious intoxication or irreversible myocardial depression[15 63] Some investigators[102,103] also noticed that quinidine reduced the membrane permeability to passive efflux of potassium in the repolarization phase The quinidine membrane binding hypothesis presented by Luchi and associates[103] appears likely and again suggests the important role of potassium ions in the genesis and termination of cardiac arrhythmias The interaction of quinidine and potassium on AV conduction reveals that lowered potassium delays conduction in the N region of the AV junction while high potassium and quinidine slow conduction within the atria and the His Purkinje system Hence the addition of quinidine in the presence of a high potassium concentration may produce AV block In contrast, the addition of quinidine in the presence of low potassium may engender AV block because of the marked slowing of conduction within the N region in the presence of a low potassium concentration as opposed to possible adrenergic effects of quinidine in this area

Similar synergistic effects can be expected when quinidine is combined with procainamide or disopyramide phosphate While these findings suggest that smaller doses of Group 1 agents can be effectively used in combination thereby minimizing the side effects of larger doses of any single agent the use of one agent in the wake of another could precipitate dangerous toxic effects[19]

In contrast to the interactions of potassium and quinidine like drugs bretylium a Group 3 agent, has another effect in the presence of a lowered potassium concentration Although bretylium tosylate is usually not selected as an initial antiarrhythmic agent, its electrophysiologic properties appear to differ from those of other antiarrhythmic agents[37,38] Bretylium tosylate besides being a postganglionic sympathetic blocking agent increases the ventricular fibrillatory threshold and has positive inotrophic effects[104 107] Wit and co workers[36] clearly identified the direct effect of bretylium on cardiac muscle as far as the effect of catecholamine release from postganglionic nerve terminals Wit felt there was no significant change in the membrane resting potential the action potential amplitude and the maximal rate of Phase 0 depolarization in the presence of bretylium[36] However he believed that the action potential duration like the refractory period, was increased.[36] Earlier studies by Watanabe and colleagues[38] clearly showed that the membrane resting potential the action potential amplitude and the maximal rate of Phase 0 depolarization were increased after the administration of bretylium and that the action potential duration and effective refractory period were decreased The decrease in action potential duration and effective refractory period were in sharp contrast to those actions of the drugs in Group 1 When bretylium is combined with quinidine the typical quinidine effects of increased action potential duration and decreased maximal rate of Phase 0 depolarization were reversed by the addition of bretylium[37]

The addition of bretylium to quinidine tended to shorten the increased intra atrial conduction time induced by quinidine but further prolonged the intranodal and total AV intervals Bretylium appears to increase intranodal conduction delay while quinidine delays conduction within the atria and the His Purkinje system Hence the addition of quinidine to bretylium significantly prolonged AV transmission time and could produce AV block in the clinical setting[37] Although Bacaner[104 105] has previously indicated that the ideal effects of bretylium could not be achieved in the presence of quinidine like agents little specific information was available until these agents were used in combination in the experimental setting[37] Hence significant antagonistic effects are produced by a combination of quinidine and bretylium with reference to the action potential duration and the maximal rate of depolarization in ventricular fibers As far as AV conduction is concerned, the action of bretylium appears similar to that of digitalis acetylcholine and low potassium in slowing conduction within the N region of the AV node[37] Group 1 drugs such as quinidine procainamide and propranolol may slow conduction in the other regions of the A V

transmission system, therefore, if these drugs are used in combination they could aggravate preexisting AV block

Little is known about the interaction of Group 2 drugs with either Group 1 or Group 3 agents The results of such combinations must be left to future studies

Interaction of magnesium with potassium

Until recently, very little information was available on the interactions of potassium and magnesium on cardiac electrophysiology,[108] except for the electrocardiographic changes produced by chronic potassium and magnesium deficiency [109] It became obvious that increased magnesium concentration in the presence of either high, normal or low potassium concentration tended to increase the action potential amplitude membrane resting potential, and maximal rate of depolarization of ventricular muscle fibers and to prolong the AV conduction time [108] These effects became even more pertinent in the presence of a high potassium concentration Reduction of magnesium concentration to one third produced completely opposite results Prolongation of the effective refractory period by high magnesium concentration was greater than that of the action potential duration this resulted in a better propagation of early premature responses A low magnesium concentration shortened the effective refractory period but tended to prolong the relative refractory period and increase ventricular vulnerability

In essence, the effects of high magnesium and low magnesium tend to be antithetical but they appear largely dependent on extracellular potassium in the presence of a normal calcium concentration [108] The possible explanation for the interaction of potassium and magnesium may involve the fact that magnesium ions appear to play an important role in the active transport of sodium and potassium across the cell membrane [110] Chronic magnesium deficiency leads to a loss of intracellular potassium while magnesium prevents this loss possibly by reducing the membrane permeability to potassium [111] However, it may be argued that if magnesium ions affect transmembrane potentials predominantly through active transport high magnesium may cause an increased intracellular potassium concentration and a higher transmembrane potassium gradient, thereby increasing the resting potential, action potential amplitude and maximal rate of depolarization This effect may then be expected to be more pronounced in the presence of higher extracellular potassium concentrations with reduced transmembrane gradients and less marked in the presence of lower extracellular potassium concentration where the transmembrane potassium gradient is already increased The fact that significant increase (by high magnesium) or decrease (by low magnesium) in the maximal rate of depolarization was seen only at the high potassium level may be explained on this basis [108] However it appears that alterations in potassium concentrations have a greater effect on the membrane resting potential, action potential amplitude and maximal rate of depolarization than do changes in magnesium concentration [108] Nevertheless it should be noted that alteration of extracellular magnesium concentration has certain effects although minor, on the ventricular action potential and AV conduction second, these electrophysiologic effects of magnesium ions are significantly modified by the extracellular potassium level The general similarity of magnesium action to that of calcium should also be considered

Summary

When one considers the complex interaction of antiarrhythmic drugs, either among the various groups or in the presence of altered electrolytes the number of possible antagonistic and synergistic actions becomes almost infinite This overview has attempted to amalgamate present information concerning drug and electrolyte interactions Fortunately in the clinical setting one is usually operating within the physiologic range for serum electrolytes and many of these alterations shown in laboratory studies may not be pertinent It should be remembered, however, that when serum electrolyte derangements are present, the usual or expected effects of antiarrhythmic drugs may be masked leading to erroneous therapy or to the conclusion that the therapy is either inadequate or useless

This summary also points out that marked beneficial effects can be achieved particularly by the use of digitalis and propranolol in slowing AV conduction in the presence of supraventricular arrhythmias and that low potassium com

pletely nullifies the action of the quinidine like or Group 1 agents

The antagonism of bretylium to quinidine like agents should alert the clinician to the possibility that the administration of Group 1 drugs in the wake of Group 3 or possibly other antiarrhythmic drugs may either nullify or aggravate certain pharmacologic actions Although it is true that quinidine lidocaine and procainamide can be used with increased efficacy in the presence of propranolol the opposite may be true when they are used in the presence of bretylium Precise monitoring of serum electrolytes would appear essential before and during antiarrhythmic drug therapy

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Fundamentals of clinical cardiology

Historical landmarks Ebstein's anomaly of the tricuspid valve

Paul Sekelj, Ph D
Bruno G Benfey M D
Montreal Quebec Canada

The congenital abnormality known as Ebstein's anomaly is today so well recognized that it can be diagnosed with confidence on the basis of physical electrocardiographic and radiologic findings alone And yet clear recognition of the features of this syndrome is a relatively recent development a fact which is somewhat surprising in the light of Ebstein s[1] complete and careful description published in 1866 Abbot s[2] 1,000 cases of congenital heart disease published in 1936 contained *no example of* Ebstein's anomaly By 1950 when Engle and her colleagues[3] reported three cases with an excellent analysis of the clinical aspects of this syndrome they could collect reports of only 20 published cases in the literature The first cases diagnosed during life were reported by Van Lingen and his colleagues[4] two years later and since then many cases have been well documented

A long delay between first description and general recognition of this anomaly might be partly attributed at least in the English speaking world to the lack of any translation of Ebstein's article from the original German into English, prior to Schiebler and associates [5] translation in 1968 We have felt that it would be beneficial to make another translation extracts of which are reproduced below It is of interest, not only as a classic example of meticulous observation and reporting, but of the deduction of disturbances of function from the disturbances of anatomy which were observed.

From the Departments of Physiology and Pharmacology McGill University and the Department of Cardiology of the Royal Victoria Hospital Montreal Canada

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Reprint requests to Dr Paul Sekelj *Department of Physiology McGill University* McIntyre Medical Sciences Building Montreal 101 Quebec Canada

Translation of Ebstein s original article

'The case to be reported here is of great interest from both anatomical pathologic and medical points of view The case is related to the insufficiency of the cusps of the tricuspid valve caused by a complete malformation of the same A similar case to my knowledge, has not previously been observed *anatomically or* described medically

"Joseph Prescher, a worker, 19 years of age was admitted to the First Medical Division of the Allerheiliges Krankenhaus on June 28 1864' Apart *from childhood illnesses there* was no real complaint until the previous year, when the patient had started *to lose weight For* eight days before admission there was swelling of the lower extremities

Physical examination revealed a 'very skinny' patient with a high degree of facial cyanosis There was edema of the lower limbs and ' marked jugular venous pulsations synchronous with the heart beats '

'In the whole area of the heart dullness one can clearly feel a superficial shock and a thrill coincident with the beginning of systole In the whole area of the heart dullness both heart sounds are obscured by a murmur which begins with systole and extends into diastole This murmur is particularly audible at the base of the heart, and can be perceived also in the frontal upper region of the thorax particularly at the right side The second sound of the pulmonary artery is not increased The murmurs described are audible also but with diminished intensity, at the posterior area of the thorax, along the line of the descending thoracic aorta The appetite is good, the tongue is slightly grayish the one or two daily evacuations are of normal color The urine



Fig 1 Right auricle and ventricle opened by incision from the margin of the superior vena cava

is without albumin Treatment consisted of internal administration of morphine to ensure that the night rest may not be disturbed by coughing Edema of the legs decreased somewhat since hospitalization Collapse soon occurred and the patient died on July 6 1864 at 5 30 A.M eight days after his admission showing symptoms of pulmonary edema.

Dr Ebstein who was both pathologist and assistant physician of the Allerheiliges Hospital, Breslau, carried out the autopsy three hours after death Of the heart he reported as follows

Translation of Ebstein's autopsy report

The right auricle (Fig 1) is considerably dilated, the m. pectinati are properly developed. The greatest thickness of the right auricular wall is 3 to 4 mm. The Eustachian valve at the insertion of the lower vena cava into the right auricle is properly developed However the Thebesian

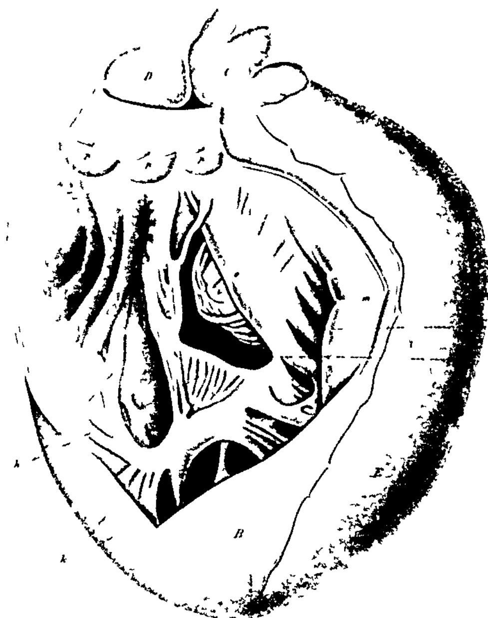


Fig 2 Right conus arteriosus opened by incision from the apex of the right ventricle (about 1 cm to the right of the longitudinal sulcus) through the anterior wall of the right ventricle into the pulmonary artery

valve at the insertion of the big coronary vein is not completely closed There are several openings in the valve of the foramen ovalis Two of them are located in the wall the largest one is on the frontal margin and measures 15 mm from above downward and 5 mm from the front to the back With its convexity to the back it is limited by a slightly thickened margin The second one in the wall is much smaller, about the size of a lentil Slightly higher there is an opening the size of a hemp seed and there are two more holes above the one described first which are not shown in the drawing

'Turning to the description of the right ventricle (Fig 2), we see immediately a thoroughly abnormal shape of the tricuspid valve The right annulus fibrocartilagineus *(e)* is perfectly normal and from it—corresponding to the frontal *(m)* and posterior *(n)* wall of the right ventricle—a membrane *(h, h_1)* arises which passes into the posterior half of the endocardium of the ventricular septum *(o)* In combination with the strongly turbid and thickened posterior half of the endocardium of the ventricular septum this membrane forms a bag which we cut open and which is connected with the rest of the endocardium or the interior of the right ventricle in the following way From the outer wall of this

membrane there emerge shorter and longer thinner and thicker tendinous fibers which pass into papillary muscles *(k)* which insert in the inner wall of the right ventricle partly with single attachment and partly splitting repeatedly These tendinous fibers and papillary muscles are almost completely absent in the upper part of the right margin and the posterior wall of the right ventricle but are numerous in the lower part and the anterior wall of the right ventricle The membrane itself *(h h_1)* looks and behaves as a fibrous tissue It is white and shiny in parts very thin and translucent in other parts somewhat thicker and it appears to be full of holes particularly in its lower part *(f)* These holes vary in size from slightly more than hemp seed up to lentil size Some of them are round, others oval and they are divided by narrower and wider fibrous bridges All the openings lead into the space between the outer face of the membrane *(h, h_1)* and the inner wall of the right ventricle Fifteen millimeters beneath the right annulus fibrocartilagineus right beneath the cutaneous part of the ventricular septum, there emerges from the endocardium a triangular flap *(i)* Its broad base is directed upward and its point downward and it has the size of a 25 cent coin The tip is connected partly with a papillary muscle *(1)* which sits freely in the cardiac cavity and mainly connected with the endocardium by numerous partly very long thin tender tendinous fibers arising partly from its tip but mostly from its posterior surface With the same 4 cm long papillary muscle is connected the anterior part of the membrane *(h)* mentioned earlier by a thin branch at its upper by a broad branch at its upper and by a broad branch at its lower part In this way a longitudinal oval opening *(r)* is formed, measuring 4 cm vertically and 3 cm. horizontally which forms the access to the right conus arteriosus *(n)* which is otherwise completely closed. The latter is shown in Fig 2 drawn in its original size with great care It is markedly dilated and its endocardium is slightly turbid. It forms an oval cavity whose anterior and lateral walls are formed by the wall of the right ventricle *(m)* and the anterior part of the ventricular septum *(o)* and whose posterior wall is formed by the anterior wall of the membrane *(h)* which particularly with its lower part, is connected with the inner face of the right ventricle *(B)* by numerous tendinous fibers and papillary muscles On the inner wall of the upper part of the right ventricle which borders with the right conus arteriosus one sees a moderate number of flat papillary muscles arising from it and soon returning to it. On the posterior wall of the right conus arteriosus one sees at *r* the opening described through which one has access to the cavity formed by the membrane *h* h_1 and the posterior part of the endocardium of the ventricular septum At *i* one sees the rudimentary flap described above which according to its position corresponds to the interior of a normal tricuspid valve The access to the pulmonary artery is completely free From the conus arteriosus downward one has a direct access to that part of the right ventricle which in addition to the right conus arteriosus is located between the outer wall of the membrane *h*, h_1 and the inner wall of the right ventricle and which communicates with the cavity formed by the membrane *h* h_1 by the holes *f* only The right annulus fibrocartilagineus has a circumference of 12 5 cm The cavity of the right ventricle is markedly enlarged its musculature has a thickness of 3 to 4 mm. The valves of the pulmonary artery are perfectly normal as is the pulmonary artery itself its circumference is 6 cm

"The left atrium is not dilated. Its endocardium is turbid. The bicuspid cusp is normal it can close and the left ostium atrioventriculare is not narrowed. The left annulus fibrocartilagineus has a circumference of 10 8 cm The valvular membrane and its fibrous tendons are slightly turbid and thickened but not shortened. Excepting the papillary muscles the musculature of the left ventricle measures 8 mm. The papillary muscles of the left ventricle are perfectly normal The cardiac musculature is yellow reddish Histologically the muscle fibers are normal. The aortic valves are perfectly normal Circumference of the ascending aorta is 6 4 cm The intima of the aorta is slightly yellow with sparse millet seed-sized inclusions The descending thoracic aorta has a circumference of 4 cm Both jugular venous cusps are normal In the cardiac cavity a large amount of blood coagulates with a beacon like surface

In his discussion of these findings Ebstein summarized the anatomical abnormalities as follows

"There are three malformations in the heart of the present case the first of which is most important, as we will soon see These three malforma

tions are (1) severe malformation of the tricuspid cusp (2) absence of the Thebesian cusp, and (3) open foramen ovale"

Malformation of tricuspid cusp

Let us first consider the first malformation (Figs 1 and 2) As outlined above there is no proper tricuspid cusp At the most there remains of it one flap namely the inner one *(i)* However, as the latter arises abnormally, below the valvular ring *(c)* as most of its tendons *(g)* lead directly into the endocardium, and as its formation is generally rudimentary, it differs from a normal flap to such an extent that we must regard it as highly stunted The anterior and posterior flaps are entirely missing We saw that in their place there is a membrane *(h, h₁)* connected with the inner surface of the wall of the right ventricle partly by papillary muscles and tendinous fibers *(b)* which all arise on the outside of the membrane The membrane *(h, h₁)* divides the right ventricle into two halves of which one comprises the bag formed by the membrane and the endocardium of the posterior half of the ventricular septum and the other is formed by the right conus arteriosus in its normal sense and the remaining space between the inner wall of the right ventricle and the outside of the membrane These two halves are connected in two ways One is the longitudinal oval opening *(r)* leading to the right conus arteriosus and the other consists of the many holes *(f)* in the membrane *(h, h₁)* that have been mentioned

Later we will discuss the effect of the malformation of the tricuspid cusp on its function We will first answer the question when and how this malformation arose It began, without doubt, at the time when the atrioventricular cusps were formed The other possibility—that fetal endocarditis led to the absence of the tricuspid cusp—nobody would accept after reading the description of our case Embryology teaches that the formation of the venous cusps occurs in the second and third fetal months The ventricular septum is completely formed in the seventh week and the ventricles communicate with the auricles by two separate openings The form of these primitive venous openings is described as extremely simple they are nothing more than plain round slits The two lips which limit each of these slits are the first indication of venous cusps At this time the margins of these cusps that are in the process of formation are already in connection with the ventricular wall however, the cusps are distinctly formed in the third month only We must thus certainly place the origin of our tricuspid cusp malformation into the time given However, we cannot say how it arose until embryology tells us more about the mode of formation of the individual flaps of the cusp, at the present time we do not know The turbidity and thickening of the membrane *(h, h₁)* and the rudimentary flap *(i)* mentioned above speak for inflammatory processes of which it is now impossible to know whether they occurred in fetal life or after birth But this has no bearing on our case Of the congenital malformations of the heart the present case seems to be one of the rarest. At least in a careful search of the literature we have not found an identical case Apart from stenosis of the right ostium venosum or insufficiency of the tricuspid cusp due to fetal endocarditis the following inborn malformations have been described The cusp is absent only when the right heart is considerably deformed. This always occurs when the venous opening of the right ventricle is closed Recently Nuhn described a case of a 6 week old blue baby with complete defect of the tricuspid cusp in addition to other abnormalities Similar cases have been described earlier by Dreysig and Schuberg Complete absence of the tricuspid cusp does not occur when the rest of the heart is normal but parts and leaflets of it might be insufficiently developed. Morgagni found in a 16 year old girl who had been sickly from youth that one leaflet of the tricuspid valve was normal and the other two were too small

Furthermore Otto remarked that, as he observed on several occasions, the development of the trileaflet valve is inhibited and it exists in part only if the aorta develops very much to the right Finally, an excessive formation has been observed several times and it consists of an increase in the number of leaflets of the venous valves This was mentioned by Haller who observed it himself and related observations by Rosen and Garengeot who noticed six instead of three leaflets Our review of the malformations of the tricuspid valve shows that our type of case has not been mentioned, as there is an excessive formation of the anterior and posterior and an insufficient formation of the inner leaflet of the tricuspid valve with an entirely abnormal

behavior of the tendinous fibers and papillary muscles on the valvular apparatus of the right venous opening

Absence of Thebesian cusp

The second malformation in our heart is the absence of the Thebesian cusp Its absence or incomplete formation is the most often noticed cardiac malformation Otto found it missing in three cases one adult patient and two newborn infants with other malformations There are many observations concerning this phenomenon Recently we found no trace of the Thebesian cusps a 75 year old woman who had fatty degeneration of the myocardium The veins in this case led into the right auricle at the normal place with two openings close together the larger one was the lower the smaller one was just above The coronary arteries both arose above the right aortic valve

Open foramen ovale

The third malformation of our heart, open foramen ovale is a very frequent occurrence among inborn cardiac malformations In 53 cases of inborn cardiac disease Gintrac found it 27 times—i e, in almost half of the cases

After thus reviewing the malformations of our case the following questions arise (1) What is their effect on cardiac function? (2) Can the signs found in vivo be explained by the anatomical findings? (3) Are the changes in other organs (tuberculosis) related to the disease of the heart?

Effect of malformations on cardiac function

Considering the first question we will disregard the deficiency of the Thebesian cusps in evaluating the anomalies of the circulation and consider merely the malformation of the tricuspid valve as the open foramen ovale is due to the latter condition and it by itself cannot alter the circulation When the right auricle in systole empties its blood into the right ventricle which is in diastole the blood flows partly into the bag closed by the membrane mentioned before and partly through the slitlike openings into the right conus arteriosus and the remaining part of the right ventricle between the outer face of the membrane and the inner wall of the right ventricle A small additional part of the blood could reach the latter location through the multiple small openings in the membrane.

During systole of the right ventricle the blood in the bag formed by the membrane is pushed back into the right auricle as there is no obstacle A small part of it only flows into the right conus arteriosus through the slit sized opening The blood in the right conus arteriosus is pushed into the pulmonary artery during systole of the ventricle Thus despite the complete insufficiency of the atrioventricular ostium, a considerable amount of blood flows into the pulmonary arterial bed. Only part of the right ventricular blood is backed up into the right auricle during systole This might contribute to the relatively long life span of the patient. The flow of blood back into the right auricle led to its dilatation and inhibited the complete occlusion of the valvula foramen ovalis This has been observed in a number of other conditions in which the flow of blood from the right heart into the lungs is inhibited.

The back flow extended beyond the right auricle into the area of the superior vena cava which was not only found to be highly dilated but which was also observed on the jugular veins in vivo which showed a pulsating movement synchronous with the heart beat Considering that at autopsy we found the valves of the combined jugular and subclavian veins capable of closing our in vivo observations could be explained according to Scoda by assuming that the wave impact (or thrust) propagates through the valves also into the following (on rushing) blood column It is remarkable that there was no congestion in the organs of the abdomen considering the amount of blood in the upper area of the vena cava The glands of the abdomen and intestinal tract showed nothing of this kind There was no albuminuria in vivo and only slight edema of the lower legs

Explanation of sounds

How can the sounds be explained—one systolic and one diastolic—which masked the heart sounds and had an intensity that caused a readily felt vibration (buzzing) of the anterior thorax wall? Has the malformed tricuspid cusp contributed to the origin of the sounds—or the first sound, if we assume that the second one is formed in the arteries and merely conducted into the cavities of the heart? We must reject this The first sound could not arise in the right ventricle in the manner generally assumed, namely by the

sudden interruption of the blood flow against the auricle due to the extension of the tri flap cusps by the blood hitting the valve (Scoda) It is most probable that the first sound heard over the right ventricle was conducted only Our highly malformed tricuspid cusp supports this statement and it also elucidates the difficulty of explaining the origin of the sounds Everything we have said must, of course, be only hypothetical It is most probable that (1) the systolic sound arose when the blood flowed back into the right auricle during the ventricular systole and there met with the blood coming from the vena cava, that is when a smaller bloodstream flowed fast into a yielding mass of blood (Hoppe, Scoda), and that (2) the diastolic sound was caused by the flow into the cavity of the right ventricle over the not so smooth inner face of the membrane mentioned earlier

Role of changes in other organs

The tuberculosis causing the death in our case could be based on a genetic disposition or it could be due to the heart disease Frerichs and others following him observed tuberculosis in the presence of inborn stenosis of the valves of the pulmonary artery Although the pulmonary arterial valves were normal in our case, the analogy is present. When the blood is backed up from the cavity of the right ventricle into the periphery, the normal amount of blood could not enter the pulmonary arterial bed. Thus in our case the tuberculosis might have an origin similar to that in the presence of a narrow right ostium arteriosum

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Acute respiratory insufficiency and cor pulmonale Pathophysiology, clinical features and management

Part I Pathophysiology and clinical features

Spencer K Koerner M D*
Robert J Malovany M D**
Bronx N Y

There is no universally accepted definition of respiratory failure With increasing impairment of pulmonary function and ventilatory reserve respiratory failure eventually occurs but the actual point has not been adequately indentified While dyspnea might be considered sufficient by some it is generally accepted that respiratory insufficiency is present when arterial blood gases are significantly abnormal Respiratory failure is sometimes divided into two types one in which there is decreased arterial oxygen tension (PaO_2) but a normal arterial carbon dioxide tension ($PaCO_2$) and the other in which there is hypoxemia along with an elevated $PaCO_2$ This discussion will refer to the hypercapneic cases but clearly extreme hypoxemia in the absence of CO_2 retention is still a life threatening situation requiring careful management. For purposes of this discussion we will define respiratory failure as a state of impaired respiratory function in which the PaO_2 is below 60 mm Hg in the absence of intracardiac right-to-left shunting and the $PaCO_2$ is above 50 mm Hg and not due to respiratory compensation for metabolic alkalemia

From the Division of Pulmonary Medicine, Montefiore Hospital and Medical Center and the Albert Einstein College of Medicine Yeshiva University

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Reprint requests to Spencer K Koerner M D Montefiore Hospital and Medical Center 111 East 210 St., Bronx, N Y 10467

*Chief Division of Pulmonary Medicine Montefiore Hospital and Medical Center and Assistant Professor of Medicine Albert Einstein College of Medicine.

**Fellow Division of Pulmonary Medicine Montefiore Hospital and Medical Center

With increasing severity of pulmonary disease cardiovascular complications set in first pulmonary hypertension and subsequently right sided cardiac hypertrophy and finally right sided congestive heart failure The term "cor pulmonale" in this context has been defined as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lung except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease"[1] Cor pulmonale then does not imply right sided failure although right sided failure develops with increasing severity of cor pulmonale

Many different conditions cause impairment of pulmonary function and can result in respiratory failure (Table I) The common denominator in all these situations is the inability to maintain an alveolar ventilation ($\dot{V}A$) sufficient to eliminate the carbon dioxide produced by the body ($\dot{V}CO_2$) This review will be limited mainly to those entities which are long standing and which gradually lead to the development of cor pulmonale By far the most common of these conditions are *chronic bronchitis* and *emphysema* and most of this discussion will therefore be particularly pertinent to these two known together as Chronic Obstructive Pulmonary Disease (COPD)

Pathophysiology of respiratory failure

Ordinarily arterial oxygen and carbon dioxide levels are maintained within a fairly narrow range This requires regulation of ventilation distribution of inhaled fresh air to alveoli diffusion of oxygen and carbon dioxide, and perfusion

sudden interruption of the blood flow against the auricle due to the extension of the tri flap cusps by the blood hitting the valve (Scoda) It is most probable that the first sound heard over the right ventricle was conducted only Our highly malformed tricuspid cusp supports this statement and it also elucidates the difficulty of explaining the origin of the sounds Everything we have said must, of course, be only hypothetical It is most probable that (1) the systolic sound arose when the blood flowed back into the right auricle during the ventricular systole and there met with the blood coming from the vena cava, that is, when a smaller bloodstream flowed fast into a yielding mass of blood (Hoppe Scoda), and that (2) the diastolic sound was caused by the flow into the cavity of the right ventricle over the not so smooth inner face of the membrane mentioned earlier

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necessary energy to increase ventilation and keep the Pa_{CO_2} at normal levels The increased CO_2 gradient allows the patient to passively blow off more CO_2 while consuming less O_2 in work of respiration leaving more available for other tissue This adaptation also causes a lowering of arterial P_{O_2} but has only a small effect on arterial O_2 saturation since the Pa_{O_2} generally falls on the flat part of the oxyhemoglobin dissociation curve This adaptation is quite dangerous as a relatively minor insult to the already compromised respiratory system causes an acute further rise in Pa_{CO_2} leading to respiratory acidosis Furthermore the P_{O_2} falls into the steep part of the oxyhemoglobin dissociation curve resulting in dangerously low oxygen saturations

Limitation in diffusing capacity Ordinarily diffusion of O_2 and CO_2 takes place quite rapidly across the alveolar capillary interface The pulmonary capillary blood is exposed to alveolar air for about 0 75 sec and equilibration of gases will have occurred in less than 0 3 sec. under normal conditions

Abnormalities of diffusion rarely result in CO_2 retention since CO_2 is 20 times more diffuseable than O_2 It is only at the terminal stage of interstitial lung disease that inability to excrete CO_2 develops Early in these conditions there is no blood gas abnormality in spite of the impairment of diffusing capacity since the time course for O_2 diffusion can be as long as 0 75 sec. before an alveolar capillary gradient occurs. As the disease progresses there is hypoxia with normal or low P_{CO_2}

Although diffusion abnormality *per se* is not a common cause of respiratory insufficiency patients with emphysema have diminished diffusing capacity (DL_{CO}) This is because of loss of alveolar septae and pulmonary capillary bed so that the entire diffusing surface area is reduced.

Ventilation perfusion imbalance The maintenance of normal blood gases depends on a balance between ventilation and perfusion (VA/Q) to all areas of the lungs In spite of the gradient that exists because of gravity with high VA/Q at the apices and low ratios at the bases the V/Q for the lung as a whole is normally 0 8 Mismatching of ventilation and perfusion is undoubtedly the most important cause of hypoxemia in the course of most pulmonary diseases. VA/Q may vary in different parts of the lung because of uneven ventilation uneven perfusion or both Pulmonary venous blood draining areas that are well perfused but poorly ventilated (low VA/Q) is inadequately oxygenated and contributes to the total venous admixture This is a shunt like effect but can be differentiated from anatomic shunt since arterial blood will be fully oxygenated after breathing 100 per cent O_2 if hypoxia is due to V/Q imbalance These areas of low V/Q are secondary to such things as pneumonia atelectasis and bronchial obstruction The P_{CO_2} of blood leaving these areas is high but the CO_2 tension of mixed arterial blood will still be normal or even low because sufficient numbers of well perfused alveoli in other areas will be hyperventilated. This compensatory hyperventilation however is not effective in correcting the hypoxemia resulting from the venous admixture due to the shape of the oxyhemoglobin dissociation curve

Excess ventilation in relation to perfusion (high VA/Q) contributes to dead space ventilation This results in a higher dead space to tidal volume ratio (Vd/Vt) with a relative decrease in alveolar ventilation Patients with very high Vd/Vt such as in emphysema may appear to be hyperventilating when in fact their alveolar ventilation may be normal or low

Since V/Q imbalance is so important in the production of hypoxia much of the therapy recommended is aimed at improving the relationships of ventilation to perfusion thereby improving blood gases

Shunts Shunts can be thought of as absolute VA/Q imbalance with VA = O Anatomic right to left shunts secondary to congenital heart disease or A V malformations may contribute to hypoxia complicating lung disease but they will not be dealt with here Absolute VA/Q imbalance occurs in pneumonia and atelectasis since compensatory pulmonary vasoconstriction does not completely shift blood flow away from areas of no ventilation. In both anatomic right to left shunts and absolute VA/Q disturbance the hypoxia cannot be corrected by 100 per cent oxygen

Pulmonary heart disease

Cardiac failure Patients with long standing severe respiratory insufficiency often develop heart failure Right ventricular failure is well established as a complication of chronic pulmonary disease while left ventricular failure is controversial but may also occur in the later stages of chronic respiratory insufficiency

Table 1 Causes of alveolar hypoventilation

A NEUROLOGIC DISEASE	
1 Depression of respiratory center	
	Primary alveolar hypoventilation
	Narcotic or barbiturate overdose
	Anatomic damage to the medulla
2 Impairment of neuronal or neuromuscular conduction	
	Poliomyelitis
	Guillain Barre syndrome
	Peripheral neuritis
	Myasthenia gravis
B IMPAIRMENT OF THORACIC CAGE MOTION	
	Kyphoscoliosis
	Arthritis
	Obesity
C PULMONARY DISEASE	
1 Restrictive lung disease	
	Idiopathic interstitial pneumonitis
	Scleroderma
	Sarcoidosis
	Congestive heart failure
2 Obstructive lung disease	
	Chronic Bronchitis
	Emphysema
	Bronchial asthma
	Obstructing lesions of the airways

of ventilated alveoli Assuming one is at sea level, abnormal PaO_2 and $PaCO_2$ develop only when these processes are impaired by disease affecting the physiology of respiration The following mechanisms are therefore the only means of developing hypoxia or hypercapnea

Hypoventilation The level of CO_2 in the arterial blood is determined by the relationship

$$P_{CO_2} = \frac{V_{CO_2}\ (ml/min.)}{V_A\ (L/min)} \times 863$$

The CO_2 tension is thus inversely proportional to alveolar ventilation and directly proportional to CO_2 production Patients with hypercapnea have an inadequate V_A for their V_{CO_2} O_2 and CO_2 are the only gases participating in respiration so that an increase in alveolar carbon dioxide (P_{ACO_2}) will result in concomitant decrease in alveolar oxygen tension (P_{AO_2}) and hypoxemia

There are three mechanisms responsible for alveolar hypoventilation (1) alteration in central respiratory control, (2) inadequate peripheral ventilatory response and (3) a combination of (1) and (2)

1 *Alteration in central respiratory control* Hypoventilation can occur secondary to CNS damage due to trauma, tumor, infection, or ischemia In patients with primary alveolar hypoventilation, the respiratory center is insensitive to increases in $PaCO_2$ in spite of normal nerve conduction and muscle strength

2 Inadequate peripheral ventilatory response Hypoventilation may result from neural or neuromuscular diseases where, regardless of stimuli from hypercapnea or hypoxia or the efferent signals from the CNS, the respiratory muscles fail to get the message as in poliomyelitis and polyneuritis or fail to respond adequately as with myasthenia gravis and muscular dystrophy A similar mechanism is operative when mechanical factors impair ventilation such as in severe asthma, acute upper airway obstruction and crushed chest injury In these situations hypoventilation may result because the bellows is unable to respond regardless of respiratory drive

3 Disturbed respiratory control response relationship

Hypoventilation occurs in advanced chronic lung disease due to pulmonary and chest wall abnormalities and also due to alterations in the respiratory control center West[2] has shown that increasing V/Q inequality can lead to a lowered PaO_2 and an elevated $PaCO_2$ as well The normal response to elevations of $PaCO_2$ however, is hyperventilation If this compensation is inadequate CO_2 retention will occur This inadequate "compensation' results from a complex interaction of factors Increasing respiratory work and oxygen cost of breathing become necessary to overcome either increasing airway obstruction or decreasing pulmonary or chest wall compliance In a normal subject the cost of an increase in ventilation is only about 1 or 2 ml of O_2 per liter of ventilation or only 2 to 8 per cent of total O_2 consumption A patient with lung disease may have inefficient lungs due to ventilation perfusion inequality and also may have to overcome increased airway obstruction or decreased compliance The oxygen consumption of his respiratory muscles can be massively increased up to 50 per cent of total O_2 consumption While a patient may be able to withstand this increased respiratory muscle O_2 consumption briefly on a long term basis this would take away needed O_2 for other vital body functions. Thus an adaptation takes place The central CO_2 responsiveness becomes blunted allowing these patients to tolerate an elevation in P_{CO_2} rather than expend the

superimposed. Chronic bronchitics on the other hand are the blue bloaters They have diffuse airways obstruction secondary to bronchial mucus gland hyperplasia and inflammation and physiologically have severe V/Q abnormalities with resultant hypoxia and eventually hypercapnia These patients have cough and expectoration developing early in life and because of hypoxemia they develop secondary polycythemia and cor pulmonale The intermediate group has features of both chronic bronchitis and emphysema

The precipitating cause of acute decompensation is not always obvious The presence of certain bacteria in the sputum during a period of exacerbation has lead to the belief that many episodes are the result of bacterial respiratory infection however signs of pyogenic infection such as fever and leukocytosis are usually absent Other etiologic factors include viral respiratory infection congestive heart failure pulmonary emboli and pneumothorax In all cases of respiratory failure a precipitant should be looked for and treated appropriately

In addition to signs and symptoms of hypoxemia hypercapnea and acidosis patients will present with clinical features of the underlying disease and precipitating factors Symptoms of hypoxia include personality changes confusion loss of judgement and ultimately loss of consciousness Symptoms of elevated CO_2 tensions are probably related to associated acidemia Thus patients with chronic hypercapnea and compensatory metabolic alkalosis can withstand fairly high P_{CO_2}s and remain relatively asymptomatic Patients who have not yet compensated may develop headache somnolence irritability and coma The mental and CNS signs and symptoms may relate to increased cerebral blood flow and elevated CSF pressure It is difficult to separate the effects of hypercapnea from those of hypoxemia

In the acute episode of respiratory failure tachycardia and systolic hypertension may develop resulting from catecholamine release Increasing hypoxemia and acidosis aggravate pulmonary hypertension resulting in right ventricular failure with associated venous distention hepatomegaly and peripheral edema Findings of cor pulmonale including a left parasternal heave and accentuated pulmonic second sound may be present but the cardiac examination is frequently made difficult by hyperinflated lungs or adventitious sounds.

Ultimately the diagnosis of alveolar hypoventilation and severe hypoxemia must be made with the help of arterial blood gas determination since the clinical assessment of P_{O_2} and P_{CO_2} is most inaccurate History and physical examination along with chest roentgenograms and ECG will usually allow for identification of the underlying disease especially when separating neurologic and muscular disorders from primary lung diseases Perhaps the most difficult differentiation is between COPD and congestive heart failure Left sided failure can impair pulmonary function is associated with hypoxemia and hypercapnia and can present with wheezing It can be responsible for all or part of the picture of respiratory insufficiency and since the therapy is frequently quite different the role of the left ventricle should be clarified early in the management of these patients If after the preliminary studies are completed, the data base is insufficient to make a proper assessment, then cardiac catheterization may be necessary Flow directed balloon tipped catheters can be inserted in the ICU and pulmonary artery wedge pressure measured as an indirect indicator of left atrial pressure and left ventricular function [11]

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There are a multiplicity of factors which contribute to the development of pulmonary hypertension in patients with pulmonary dysfunction Hypoxia is the most potent stimulus to pulmonary arteriolar vasoconstriction and is therefore paramount in the development of pulmonary hypertension[3] While the vascular bed can be reduced by as much as 2/3 without elevation of pulmonary arterial pressures in normals loss of capillary bed is a factor in the production of pulmonary hypertension in patients with COPD, particularly emphysema Elevated airway pressure and air trapping as well as acidemia result in further increase in pulmonary vascular resistance Secondary polycythemia with increased blood volume and viscosity also contributes to an elevated vascular resistance In order to overcome the high vascular resistance the right ventricular work increases leading to cor pulmonale With increasing severity of hypoxia right ventricular failure may be superimposed on cor pulmonale

The left ventricle The question of left ventricular involvement in chronic pulmonary disease has been debated for many years One school of thought has held that cardiac hypertrophy complicating chronic pulmonary disease involved only the right ventricle and that left ventricular dysfunction, if present, was due to concurrent valvular disease systemic arterial hypertension, coronary disease, or some other independent process Representing this viewpoint Davies and Overy[4] as well as Williams and colleagues[5] performed right and left heart catheterization in patients with cor pulmonale and failed to find any evidence of left ventricular hemodynamic abnormality There have been reports of left ventricular hypertrophy at autopsy[6] but measurements of ventricular thickness and/or weight are often unreliable and certainly give no information as to the functional status of the heart during life Other catheterization studies have shown elevations in pulmonary arterial wedge pressures and left atrial and left ventricular end diastolic pressures[7,8] in patients without obvious precipitating causes of left ventricular disease supporting the thesis that left ventricular hypertrophy and failure can result from chronic pulmonary disease The mechanisms which have been proposed to explain the occurrence of left ventricular hypertrophy in chronic pulmonary disease include abnormal blood gases particularly hypoxemia expanded collateral circulation to the lungs (left to right shunts), and interference with left ventricular function by an hypertrophied or failing right ventricle Massive enlargement of the right ventricle and right ventricular failure from causes other than chronic pulmonary disease have not been associated clinically with left ventricular hypertrophy or dysfunction Proliferation of bronchopulmonary anastomoses, especially between bronchial arteries and pulmonary veins, could be a cause of increased left ventricular output but this does not appear to be a frequent occurrence except when chronic bronchitis and emphysema are complicated by bronchiectasis[9] The best explanation for left ventricular hypertrophy and dysfunction holds that if arterial hypoxemia, hypercapnia, and acidosis are severe for a protracted period oxygen delivery to the myocardium may be inadequate and in response both ventricles may hypertrophy In episodes of respiratory failure the resulting myocardial dysfunction may contribute to respiratory distress Pulmonary congestion results in mismatching of ventilation and perfusion and increases respiratory work, thereby aggravating an already life threatening situation This may explain the improvement in blood gases which occasionally occurs when such patients are treated with diuretics[10]

Clinical features of respiratory failure

The diseases most likely to result in episodes of respiratory failure with hypercapnia are listed in Table I It has been mentioned that the great majority of admissions for decompensation are patients with COPD This general category has been subdivided into two very distinct entities *chronic bronchitis* and *emphysema* and one intermediate group possessing features of both the above Patients with emphysema are the pink puffers' Their symptoms usually start late in life and may be limited to dyspnea without cough or expectoration Emphysema is characterized anatomically by alveolar destruction and loss of capillary bed while bronchial abnormalities are absent Physiologically these patients have relatively well preserved balance of ventilation and perfusion and do not therefore have severe degrees of hypoxia As a result they do not develop secondary polycythemia or cor pulmonale unless pulmonary infection is

and was complicated by the fact that the normal mechanisms of persisting immunity to viruses are unknown immunological memory may be involved and/or the virus or its antigens may persist The increased virus antibodies in SLE can be interpreted in two ways

1 They are primary and thus SLE may be caused by more than one virus Against this is the moderate degree and multiplicity of the elevations and that high titers to several viruses tend significantly to occur in the same individuals[20 24]

2 The elevations are secondary similar to the multiple tissue autoantibodies found in SLE If so they were not due to autoantibodies nonspecifically interfering in the virus antibody test[20] On the other hand depressed cellular immunity might allow abnormal persistence of multiple viruses or perhaps more frequent reinfections thus stimulating higher antibody levels Although evidence is not available to exclude the latter our studies indicate that hyperimmunoglobulinemia is the proximate cause of the antibody elevations in SLE High IgG levels were found to correlate with high virus antibody levels and changes in IgG levels of individuals followed for years were frequently accompanied by corresponding virus antibody changes[20 24] These findings have not yet been adequately evaluated by others but we also have similar results in another CTD juvenile rheumatoid arthritis[20] Thus it seems that whatever usually stimulates the humoral immune system in SLE to produce more immunoglobulins includes virus antibody producing clones also However in any individual IgG level is a relatively weak predictor of virus antibody levels other factors, such as remoteness of infection and frequency of reinfection are no doubt more important By inference in population studies of other diseases in which polyclonal hyperimmunoglobulinemia occurs moderate virus antibody elevations should be interpreted cautiously[20]

The virus hypothesis in SLE is not of course disproved by the failure of recent efforts to identify a virus this can be blamed on not using the appropriate perhaps not yet developed methods Other factors must also be involved in the genesis of the CTD but chronic virus infection seems the most likely initial event, and probably the one most amenable to eventual therapeutic and prophylactic intervention Thus the virus hypothesis continues to attract supporters, but new approaches will likely be needed to solve the fascinating enigma of these diseases.

Paul E. Phillips M D F A C P
Assistant Professor of Medicine
Cornell University Medical College
Hospital for Special Surgery
535 E. 70th St.
New Yo k N Y 10021

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Annotations

Viruses and systemic lupus erythematosus

The idea that occult microbial infection might cause the connective tissue diseases (CTD) is not new but has again become popular because of the increased understanding of chronic (persistent latent or slow) infections particularly viral in man and animals [1-4] The hypothesis in the CTD is that when a virus (or perhaps other microbial) infection usually eliminated by most individuals occurs in somehow predisposed individuals it can become chronic i e the virus or its antigens persist in the host perhaps lifelong The virus if replicating may incorporate host cell constituents in its envelope or if latent may otherwise alter them so that the host immune system no longer recognizes them as self antigens Host B immunocytes then produce antibodies against these neoantigens which combine either in the circulation to form immune complexes or within tissues. These immunologic reactions activate inflammation, the pathologic results of which manifest as the clinical syndromes recognized as CTD

Exactly how each CTD fits into this hypothetical framework is of course unknown Major unanswered questions are

1 The identity of the microbial agent e g could it be a viroid the proposed new class of subviral agents [5] and might more than one agent cause the same clinical syndrome in different individuals?

2 The epidemiology of infection e g could it be vertically transmitted from mother to child and how common or rare is infection?

3 The course of infection e g might it occur years before and persist into the time of clinically apparent disease and which tissues are infected initially which later?

4 Any host factors predisposing to chronic infection e g are they genetic and/or environmental? Genetic factors must be important in the CTD whether or not virus infection is involved [6] Expression of immunologically mediated diseases in animals varies greatly in different inbred strains[7] family clusters of immunologic disturbances are common in man[6] and common histocompatibility antigens have been found in certain CTD e g ankylosing spondylitis [8] Likewise environmental influences must be important recognized ones in systemic lupus erythematosus (SLE) include photosensitivity and certain drugs

5 The nature of the aberrations of the host immune system allowing establishment of chronic infection e g how is cellular immunity involved? Tuberculin sensitivity is frequently depressed in the CTD[9 10] if cellular immunity to all antigens were depressed this could be the primary factor allowing establishment of chronic infection However since common viral infections appear to be handled normally before onset of the connective tissue disease chronic infection more likely causes the depression of cellular immunity perhaps analogous to the transient depression of tuberculin sensitivity during many common acute virus infections [11] Or as may occur in New Zealand mice [12] a virus might replicate in T immunocytes preferentially resulting in their failure to respond to other antigens normally Another possibility is that such failure might result from the competition for T cell response by viral antigens persisting elsewhere

Whatever the answers to the preceding and other basic questions an idea basic to the virus hypothesis in the CTD is that cellular damage results not from virus multiplication per se as in common acute virus diseases but instead results from the host immune response to the persistent virus The scientific basis for this rests on what is known about the pathogenesis of the CTD about known acute and chronic virus infections and more particularly about the role of chronic virus infection in immunologically mediated diseases of animals like the New Zealand mouse [1-4 7,13] More direct support has come from the recent finding of persistent Australia antigenemia in some patients with polyarteritis nodosa[14] and of a striking elevation of toxoplasma antibodies in some patients with polymyositis.[15] The only serious competition to the virus or more broadly stated microbial hypothesis is based primarily on epidemiologic evidence and postulates that somatic mutations result in forbidden clones of immunocytes producing autoantibodies and thus autoimmune disease [16] However one mechanism by which such forbidden clones might arise considering the possibly universal vertical transmission of oncornaviruses (causing leukemia and sarcoma) in mammals,[17] is activation of a latent virus If this occurred in T cells they might then fail to eliminate forbidden B cell clones arising by somatic mutation Or as discussed above such clones might arise as a direct response to virus altered host cell constituents Thus the virus and forbidden clone hypotheses may not be mutually exclusive

The search for a virus causing SLE was particularly stimulated by the clinical and serologic similarities of New Zealand mouse disease and human SLE [3 13] and by the electron microscopic finding of virus like structures in SLE kidneys [18] although it now seems unlikely these are in fact viral [3 6 19] Virus isolation studies have not been rewarding to date [19] but higher than normal levels of antibodies against various viruses are found in SLE the cause of which is controversial [3 6 19 21]

The study of virus antibody levels in SLE sera was initiated in the hope of finding a single striking elevation such as that which led to the identification of chronic measles infection in subacute sclerosing panencephalitis [22] However it soon became apparent that many virus antibodies were high in SLE The most usually found and/or striking elevations were to some RNA viruses in the paramyxo reo corona and toga virus groups and to the DNA viruses herpes simplex[3 6 19 20] and variably Epstein Barr [21 23 24] Different laboratories reported somewhat differing results probably due to differences in the size composition and matching of the SLE and control populations and in the methods used for measuring virus antibodies and for statistical analysis Nevertheless the over all picture was of small to moderate although frequently significant increases of antibodies to many viruses unrelated taxonomically Thus the hoped for clue to a single virus causing SLE did not emerge

The cause of the multiple antibody elevations was unclear

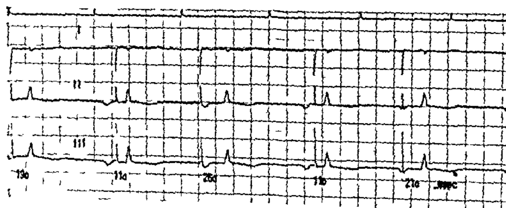


Fig 1 Measuring of the delivery refractory period (Barold[1]) by stimulation with subthreshold impulses The second and the fourth spontaneous heart action do not inhibit the pacemaker the smallest distance between pacemaker stimulus and sensed spontaneous heart action is 190 msec

Table I Measurements of the duration of D R (double reset) and of the time difference between stimulus and the top of the T wave of the antecedent action showing a correlation between these parameters

No	Patient	Distance between stimuli		Duration of reset (msec.)	Time difference between stimulus and top of T wave (msec.)	Duration of reset and top of T wave referred to one another (msec.)
		Without reset (msec.)	With reset (msec.)			
1	Bec	700	1 000	300	300	± 0
		800	1 100	300	300	± 0
		940	1 240	300	320	+20
2	Ben.	780	1 140	360	340	+20
3	Br	760	1 080	320	360	-40
4	He.	580	840	260	290	-30
		680	940	260	290	-30
5	Le	800	1 140	340	360	-20
6	Lor	680	990	310	320	-10
		800	1 120	320	320	± 0
		960	1 280	320	320	± 0
7	Mö.	760	>1 020	>300	>300	
8	Sch.	660	980	320	280	+40
		760	1 100	330	280	+50
9	We	760	1 100	340	320	+20
	Median			320	320	± 0

(Table I) Moreover it was found that the duration of the reset corresponded to the time to the top of the T wave the median of this time being 320 msec too with a range of 280 to 360 msec This means that the origin of D.R. always occurs during repolarization.

These results lead to the following explanation (Fig 2) During pacemaker stimulation a small area of myocardium is directly excited by the impulse at the negatively polarized different electrode the size of depolarized muscle area depending on the intensity of current of the pacemaker generator From this area the excitation spreads through the slowly conducting myocardium so that the indifferent electrode is reached by the excitation some 1/100 to some 1/1 000 second later At high intensity of current the excited muscle area is larger the distance to the second electrode and thus the time of conduction shorter than at low intensity This small delay

Of the fundamental aspects of the aging process

By far the greatest expenditure of money and time on the study of aging has been and still is concerned with the study of diseases of old people Relatively few new fundamental ideas concerning the aging process have evolved, and a considerable amount of repetition of work already done occupies the time and effort of many people These studies may have some value but none will solve the problem of aging delay senescence significantly or even modify or delay the onset of aging and its related diseases Unless more effort in research is directed toward the fundamental mechanisms of aging and unless attempts are made to learn how to delay the aging processes the life expectancy of man and the prolongation of an active and productive life of man will be modified little if at all It must be recognized that man lives no longer any more[1] in spite of the research and effort of the past generation

The discovery of the *juvenile hormone* of insects[2] seems to be the first and most promising advancement in the understanding of the fundamental mechanism of aging itself This super hormone[2,3] is of utmost importance It will prolong the life of insects severalfold. If such a chemi al agent can produce this effect in insects, why not expect that a yet unknown hormone can do the same in man? Imagine a hormone (polypeptide or polypetide complex) that could produce a status quo in man so that he will not age for 100 or more years or one that could extend the life span of man tenfold. Who would have thought that such a hormone existed even for insects? This finding for insects may also apply to man! Practically all of the work in gerontology and geriatrics today lacks imagination concerning the fundamental phenomenon of aging the aging process and certainly most of the results of these investigations will extend the life span of man extremely little Shouldn t something be done to change this? Imagine what might happen to the rate of graying hair wrinkling of skin aging of joints lungs heart blood vessels, brain, and all tissues if a juvenile hormone were found for man Research directly related to the fundamental aspects of the aging process must be encouraged and supported.

George E. Burch, MD
Tulane University School of Medicine
1430 Tulane Ave.
New Orleans La. 70112

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"Double reset" of demand pacemakers A different explanation of its cause

In 1971 Beller and Pupillo[4] reported a case of pacemaker (Medtronic 5840) delay by stimulation with high intensity of current (more than 12 ma) Barold and colleagues[2,3] termed this phenomenon double reset (D R) and suggested that it is caused by the stimulus after potential which in case of high stimulus energy and a short delivery refractory period of the pacemaker is sensed by the pacemaker beyond its refractory period like a spontaneous action potential

We found the same D R with the Medtronic 5840 pacemaker[6] and investigated the phenomenon in 16 patients

The following bipolar and unipolar electrodes were used unipolar Elema EMT 588 Vitatron MIP 2000 bipolar temporarily epicardial fixed electrodes after heart operation and electrode catheter USCI 6F with a distance of 25 mm between the electrodes the latter being stimulated both bipolar and unipolar as well as with reversal of the poles Pacemaker generators were Medtronic 5840 and 5880 and Biotronik EDP

Of these pacemakers only the Medtronic 5840 showed a D R Of the electrode catheters used a pacemaker delay occurred only with the USCI 6F and here only with cathodic stimulation at the tip of the electrode (9 patients) That argues against Barold and Carroll s explanation[2] since D R should take place also with unipolar stimulation and with reversal of the poles if electrochemical phenomena alone are the reason

The duration of the D R varies from patient to patient A reset however induced by the pacemaker refractory time should be constant We therefore measured the delivery refractory period of our test pacemaker by subthreshold stimulation Following a stimulus the earliest observed inhibition of the pacemaker by a spontaneous heart action was 190 msec (Fig 1) If one follows Barold and Carroll s calculation[2] adding to this time 70 msec as the delay of entrance of the current into the pacemaker the duration of the reset should be 260 msec Our results however showed a range of the delay from 260 to 360 msec and a median of 320 msec

connection with real fruit To determine whether such drinks contain valuable amounts of potassium the beverages of 100 inpatients were sampled. Only three were using real fruit juice—all voluntarily When the other 17 different products were analyzed, only one (a blackcurrant drink) had a K/Na ratio greater than unity (2 45 with K = 25 mEq per liter) The others had K/Na ratios from 0 19 to 0 32 (maximum K = 8 9 mEq per liter)

The normal dietary intake of potassium is 40 to 100 mEq daily To increase this by an additional 50 mEq 2 to 20 L. of these proprietary drinks would need to be consumed. Almost all of them are designed to be diluted 1 5 before consumption.

Commercially available 100 per cent squeezed fruit juice is rich in potassium and low in both sodium and calories (200 to 500 calories per liter) It is, however relatively expensive compared with potassium containing drugs and would need to be consumed in quantities of a liter or more daily to provide an additional 50 mEq (Table I) There is no value in the use by the majority of patients of cordials and squashes

Among foods bananas are probably the best low calorie (850 calories per kilogram) and inexpensive source of potassium. Other foods high in potassium either are expensive or contain many calories or both

We must remember that there is doubt as to the ability of the body to retain potassium at all while receiving kaliuretic agents

If an attempt at replacement is to be made there is no satisfactory alternative to potassium chloride preparations for availability cheapness and low calorie content

M C Bateson
Department of Therapeutics
Westminster Hospital Group
London England

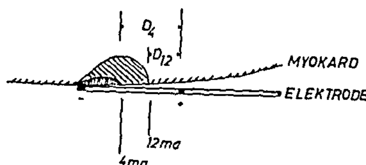


Fig 2 Schema for the electrophysiological explanation of the D R (double reset) At low intensity of current (4 ma) the distance between primarily depolarized myocardium (*MYOKARD*) and indifferent electrode (*ELEKTRODE*) (D_4) is larger than the distance (D_{12}) at high intensity (12 ma) For details see text

occurs also during repolarization Between both poles during repolarization as well as depolarization a potential difference exists which disappears after some milliseconds and may be sensed by the pacemaker as a signal in the physiological range causing a D R The fact that this happens only at high intensity of current means that only under those conditions the simulated frequency is high enough to pass the entrance of the pacemaker

In conclusion we believe that the so called "double reset" is an unusual form of T wave inhibition.

Hans P Richter v Arnauld, MD
Ulrich Kirsch, MD
Karl W Westermann, MD
Charlotte Gauwerky MD
Division of Cardiology
2nd Department of Medicine
University of Hamburg
2 Hamburg 20 Federal Republic of Germany

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Dietary potassium and diuretic therapy

Many diuretics cause potassium depletion Attempts are often made to replace this loss with potassium chloride supplements or potassium sparing diuretics According to one school of thought potassium may be replaced by simply adjusting the diet—which usually means advising the patient to eat fruit or drink fruit juice with no medical supervision

Most people do not squeeze their own fruit juice they use proprietary products many of which have a very tenuous

Table I Potassium and sodium contents of some foods

Product	*Potassium (mEq/L.)*	*Sodium (mEq/L.)*	*Amount containing 50 mEq K+*
Squeezed fruit (orange lemon grapefruit)	41 5 49 0	1 0 2 5	1 000 1 200 ml.
Commercial real fruit juice			
Grapefruit	58 5	2 5	1 400 ml
Orange	50 0	0 4	1 000 ml
Apple	32 5	1 4	1 600 ml
Grape	32 5	1 9	1 600 ml
Pineapple	56 5	1 9	800 ml
Tomato	81 5	102 5	600 ml
Nuts (e g peanuts)	151 5	1 1	340 Gm
Dried fruit (e g prune pulp)	195 0	2 6	30 40 prunes
Milk chocolate	107 0	52 5	450 Gm
Banana pulp	115 0	0 2	4 6 bananas

tensively investigate i e they were different precisely because they presented indications justifying catheterization. But such indications should, by traditional reasoning yield a relatively high prevalence of S_4 (if its presence is an unfailing sign of disease) Why was this not the case? Put differently why was S_4 uniformly associated with disease in Dr Wayne's patients and not in ours? I think the answer may lie not only in population differences but also in differences in instrumentation.

Dr Wayne cites S_4 recorded at 50 and 25 Hz. (Unless there has been an unreported breakthrough in standardizing the PCG his "2 to 3 mm amplitude" is puzzling We can obtain this and larger fourth heart sounds by simply raising the gain.) The normal filter peaks of 25 and 50 Hz suggest either Mannheimer filters or more likely Hewlett Packard or equivalent filters. We too use a Hewlett Packard system for most of our hospitalized patients and, while we find and S_4 in more normal subjects than Dr Wayne does we too get nothing like the prevalence found in our epidemiologic studies The latter employ Mass and Weber filters, particularly in nominal ranges of 35 and 70 Hz. The peak amplitudes and rolloff characteristics of these filters are markedly different from the Hewlett Packard and comparable systems. Also we find our base lines are much more noise free so that we can get clean phonocardiograms at higher relative gain. It is not surprising therefore that any fourth heart sounds visible with less sensitive equipment are more likely to have frequency amplitude characteristics produced by disease and this also conforms to our experience I do not doubt that Dr Wayne is correctly interpreting his data, but those data are based on the characteristics and limitations of his instruments.

David H. Spodick, M.D
Department of Medicine
Tufts University School of Medicine
Boston, Mass. 02130

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Obstructive cardiomyopathy

To the Editor

The paper entitled "Radiological patterns of obstructive cardiomyopathy of the left ventricle in childhood," by C. Pernot and associates, which appeared in the October issue of the JOURNAL, p. 452 fails to a great extent to add any useful information to that already available about this disease [1-4]

Obviously the authors have had an unusual opportunity to examine five infants with this disease however from the introduction it seems that they do not differentiate clearly between idiopathic hypertrophic subaortic stenosis and secondary hypertrophy e g that due to discrete subvalvar or valvar stenosis The accuracy of cardiothoracic ratio in small infants has been repeatedly questioned[5,6] and so much stress on this point did not help to prove anything new except that the heart is larger than normal In those cases with mitral regurgitation it is not reported whether or not the patients were free from premature beats during the injection of contrast material. The measurements made in Table II do not give any values for S D nor is it clear from the text where specifically these measurements were made from and what assures their reproducibility Finally the authors fail to cross reference many statements made in the text Actually only three of the 20 references are quoted in the text

J G Shakibi, M D
2000 Glenwood Ave
Joliet Ill. 60435

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Reply

To the Editor

I read with interest the letter of Dr Shakibi and I wish to answer his questions

For us the angiocardiographic patterns of idiopathic hypertrophic subaortic stenosis are similar to those of secondary hypertrophy e g that due to discrete subvalvar or valvar stenosis.

The accuracy of cardiothoracic ratio granted is not excellent but it is sufficient in practice for children six months of age or more i.e eight out of our nine cases The value of the ratio can be discussed for case 2 (infant of 3 months) whose index of 0 62 is however a reflection of cardiomegaly

Of course mitral regurgitation has been reported only in patients free from premature beats during the injection of contrast material

The measurements in Table II have been made from roentgenograms after correction of the magnification factor

Prof C. Pernot
29 Ave. du Marechal de Lattre de Tassigny
Nancy France

Letters to the Editor

Significance of the fourth sound

To the Editor

In the article by Spodick and Quarry on the Prevalence of the fourth heart sound by phonocardiography in the absence of cardiac disease (Am Heart J 87 11 1974) the authors claim the fourth sound (S_4) is equally prevalent in individuals with and without heart disease They state that an S_4 in older individuals appears to be a normal phenomenon

I find it hard to accept their method for excluding heart disease in the subjects studied. They state Heart disease was excluded by absence of appropriate history and of abnormalities of the following physical examination by two physicians ECG and chest x ray I appreciate that their subjects were from the Framingham Study and had been followed for prolonged periods Nonetheless, it is common knowledge that even extensive disease may exist in the absence of symptoms and physical findings and with a normal ECG It is a safe assumption that mild to moderate heart disease is widely prevalent in the similar absence of findings Their claim that heart disease was absent in the subjects studied would have been more believable had those individuals been subjected to further studies

During the past seven years we have had the opportunity of examining several hundred patients past the age of 35 with recordable and/or audible fourth heart sounds The majority of these patients have been extensively studied with both resting and exercise phonocardiograms apexcardiograms systolic time intervals hand grip testing bicycle ergometry and coronary cinearteriography We have rarely failed to find evidence of left ventricular dysfunction when an S_4 is recorded at 50 Hz. Even an S_4 recorded only at 25 Hz if it is more than 2 to 3 mm in amplitude is almost always accompanied by an abnormality in one or more of the above noted test procedures Of considerable interest, too was the observation that in half of our patients with documented coronary occlusive disease an S_4 could not be recorded phonocardiographically[1] In conclusion therefore I submit that the authors have not substantiated their claim while our own work supports the concept that an S_4 is a pathologic finding

Howard H Wayne MD
Director Department of Echocardiography
San Diego County Heart Center
Donald N Sharp Memorial Community Hospital
San Diego Calif 92123

REFERENCE

1 Accuracy of the phonocardiogram apexcardiogram and systolic time intervals in patients with ischemic heart disease Presented at the Regional Meeting of the American College of Physicians Palm Springs Calif Feb 22 23 1973

Reply

To the Editor

While Dr Wayne s criticisms have a certain general validity they deserve closer scrutiny as to whether they apply to our results Indeed, the absence of stress tests and invasive studies was considered in the design of our essentially epidemiologic investigation. We utilized an elaborately blinded protocol to eliminate observer biases Thus, it is extremely unlikely that the statistically equal prevalence of fourth heart sounds in clinically identified patients and clinically healthy control subjects was either a chance or a false occurrence By Dr Wayne s standards for S_4 this would imply a prevalence of occult heart disease in clinically healthy older persons which is exactly the same as that of overt heart disease in the same age range. Hardly likely However this unlikely conclusion would hinge on the traditional interpretation of the significance of the mere presence of an S_4 And this is the crux of our differences—because the respective prevalences of S_4 were determined from blindly interpreted phonocardiograms which unquestionably showed fourth heart sounds (cf criteria for S_4 and illustrations[1]) Moreover in a younger population using entirely different microphones and printouts, but the same filter system we have demonstrated identical prevalences of S_4 in ambulatory hypertensive persons and age and sex matched control subjects[2] (Naturally this protocol also followed a stringently blinded design)

I have no reason to doubt Dr Wayne s personal experience with S_4 However it appears to conflict not only with our results, but more directly with those of Benchimol and Desser[3] who found an equal (75 per cent) prevalence of S_4 in catheterized hemodynamically normal persons. *Utilizing* a blinded protocol Aytan and Prakash[4] also found identical prevalences of S_4 in patients and matched normals. Bergman and Blomqvist[5] found not only nearly comparable resting S_4 prevalence but nearly identical prevalences (over 80 per cent) of stress provoked fourth heart sounds in coronary patients and both age matched normals and younger normals undergoing isometric handgrip

Although Dr Wayne does not cite appropriately controlled studies designed to minimize observer biases our differences can be more easily explained. When experienced observers disagree the explanation may not necessarily result from faulty investigation but rather from different methodology Conflicting results need not be at odds if they are based on different study populations, or if they employ different methods or both Our patients who were unselected were drawn from an ambulatory population routinely followed for over 20 years There were certainly no indications and therefore no excuse to submit clinically healthy persons to the hazards of catheterization and angiography Any population subjected to what Dr Wayne enumerates as extensive investigations" is by definition biologically different from a normal population by virtue of whatever evidence led to the decision to ex

cluded that these procedures increased the efflux of noradrenaline via a carrier mediated process that was inhibited by cocaine and desipramine The results obtained could not be ascribed to an inhibition by cocaine and desipramine of re uptake of [^{3}H]-(−) noradrenaline since the addition of these drugs alone did not alter the rate of efflux significantly

The results of our studies of the efflux of [^{3}H]-(−) noradrenaline from adrenergic neurones suggest that cocaine may inhibit the indirect actions of these amines in the following manner phenylethylamines and phenylethanolamines may diffuse passively across the plasma membrane of adrenergic neurones as a consequence of their lipid solubility It is proposed that the noradrenaline they subsequently displace from the intraneuronal storage vesicles effluxes from the neurone via a membrane carrier and that this efflux process is inhibited by cocaine, thus antagonizing the indirect sympathomimetic responses to such agents Ross and colleagues[8] have also suggested that cocaine may inhibit the outward passage of released noradrenaline

These findings also have implications for those indirectly acting sympathomimetic amines that are transported into adrenergic neurones via the membrane pump (i e phenolethylamines and phenolethanolamines) It is suggested that the noradrenaline they displace from storage vesicles also effluxes from the neurone via a membrane carrier At physiological pH noradrenaline exists mainly as a cation[18] and efflux on a carrier would be a more efficient and rapid process than passive diffusion alone In terms of this model, cocaine would inhibit the action of such agents not only by limiting their transport into adrenergic neurones but also by inhibiting the efflux of displaced noradrenaline

David M Paton, M.B. Ch.B
Department of Pharmacology
University of Alberta
Edmonton, Alberta, Canada

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New technique for retrograde catheterization of stenosed aortic valve

To the Editor

Recently it has come to our attention that a technique for negotiating the severely stenotic aortic valve that we pres ently use in our cardiac catheterization laboratory has not been reported in the literature We would like to share this technique with you in this communication

Using the Judkins procedure for left heart catheterization we have found that a left coronary artery catheter positioned in the left coronary sinus of Valsalva in such a way that the orifice of the catheter lies above the left coronary artery will allow a 0 038 straight guide wire to be directed across the valve The coronary catheter is then advanced across the valve and a 260 cm exchange wire is threaded through the catheter and left in place in the left ventricle while the left coronary catheter is removed and replaced by a pigtail ven triculography catheter

The patient is placed in the left anterior oblique position and the fluoroscopy should be at peak magnification in order to obtain maximum detail during manipulation The guide wire is extended several centimeters beyond the catheter tip This partially straightens the catheter yet due to its pre molded configuration it remains directed toward the left cor onary sinus the soft tip of the guide wire is then used to ex plore the aortic valve region.

The cone like configuration of the deformed valve with its systolic jet tends to deflect other catheters into the dilated right coronary sinus To the contrary the jet does not deflect the soft tip of the guide wire hanging from the partially straightened left coronary catheter It usually causes the guide wire to visibly shudder providing an additional land mark for locating the stenosed valve orifice

This technique has allowed us to traverse the aortic valve in approximately 50 cases of significant aortic stenosis with gradients ranging up to 175 mm and so far there have been no cases in which the method has failed Once familiar and confident in this approach the operator can cross the valve with very little delay Its reliable success seems to hinge on the fact that the premolded left coronary catheter is not deflected toward the right coronary sinus even when the tip is partially straightened with the guide wire In that regard it differs from other catheters which are commonly used to cross the stenotic aortic valve by the retrograde approach

John R Arnold MD
Donald J Fraser MD
Michael A Nocero Jr MD
500 E Colonial Dr
Orlando Fla 32803

Mechanism of inhibition by cocaine of action of indirectly acting sympathomimetic amines

To the Editor

Many phenethylamine derivatives produce all or part of their pharmacological responses through the release of noradrenaline Of these indirectly acting sympathomimetic amines the action of tyramine has been most thoroughly in vestigated [1] In order for tyramine to act it must first be transported into adrenergic neurones by a cocaine sensitive, carrier medicated process, present in the plasma membrane This transport process is generally considered to be responsi ble for the re uptake of noradrenaline following nerve stimulation [2] Tyramine is then taken up from the cytoplasm of the neurone into intraneuronal storage vesicles where it displaces noradrenaline from binding sites The displaced noradrenaline does not apparently leave the neurone by ex ocytosis [3] but rather appears to pass through the cytoplasm before leaving the adrenergic neurone and consequently is at least partially deaminated intraneuronally [1] The well known ability of cocaine to antagonize the indirect pharmacological effects of tyramine[4] is generally considered to be due to the ability of cocaine to competitively inhibit the transport of tyramine into adrenergic neurones [1 2] (The mechanism of ac tion of many sympathomimetic agents has been recently ex tensively reviewed by Trendelenburg [1])

This model does not however appear to account for the ac tions of all indirectly acting sympathomimetic amines. β Phenethylamine phenylethanolamine phenylpropanola mine amphetamine and ephedrine all act at least partially indirectly since their pharmacological actions were reduced when animals were pretreated with reserpine [5 6] The uptake of these amines into peripheral tissues differed from that of tyramine and noradrenaline in a number of respects, the most striking being that their uptake was not inhibited by cocaine or noradrenaline [7 11] Some have therefore con cluded[7 8 10 11] that these amines, lacking a phenolic hydroxyl group are not transported into adrenergic neurones by the membrane pump or uptake process utilized by noradrenaline and tyramine In contrast others have sug gested[9] that these amines do indeed enter adrenergic neurones via the membrane amine pump but because of their high lipophilic properties they rapidly diffuse out of the neurone or alternatively that their uptake into neurones is masked by uptake into extraneuronal tissues.[1 9] If these phenethylamines and phenylethanolamines are indeed not transported into adrenergic neurones by the cocaine sensi tive membrane pump it is difficult to understand how their pharmacological actions are antagonized by cocaine [1 5 12 13]

How then does cocaine antagonize the action of indirectly acting sympathomimetic amines such as amphetamine ephedrine phenylpropanolamine phenylethnolamine and β phenylethylamine? It seems possible that recent stud ies[14 17] we have made of the characteristics of efflux of [^{3}H] (−) noradrenaline from the cytoplasm of adrenergic neurones may have a bearing on this problem In these stud ies isolated atria from reserpine pretreated rabbits were loaded with [^{3}H] (−) noradrenaline ($5\,8 \times 10^{-7}$ M for 60 minutes after inhibition of monoamine oxidase and catechol o methyl transferase After efflux for 40 to 50 minutes the subsequent efflux of amine occurred predominantly from a single intraneuronal compartment Addition of certain phen ethylamine and tryptamine derivatives accelerated efflux possibly by an accelerative exchange diffusion mechanism Efflux was also markedly increased by ouabain metabolic in hibition lowering the external Na^+ concentration or omit ting K^+ from the medium the increases in efflux so produced were all inhibited by cocaine and desipramine It was con

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Advances in Cardiovascular Surgery Edited by John W Kirklin, M D New York, 1973 Grune & Stratton Inc 279 pages Price $15 75

This publication on Advances in Cardiovascular Surgery edited by Kirklin is one of the Clinical Cardiology Monographs. There are 20 different aspects of Cardiovascular Surgery presented under three major headings, namely Congenital Heart Disease Vascular Heart Disease and Ischemic Heart Disease The various aspects of cardiovascular surgery discussed include long term follow up results of surgically treated patients, present day practices and new developments in technique and selection of patients for surgery The contributors originate from American and foreign institutions all experts in their respective fields of interest. This book is another excellent contribution to the cardiologic literature Internists and cardiologists as well as surgeons will find this book useful

Early Phases of Coronary Heart Disease Edited by Jan Waldenstrom Tage Larsson and Nils Ljungstedt Stockholm 1973 AB Nordiska Bokhandelns Forlag 362 pages. Price 53 Sw Kr

These collected papers were presented at the Seventh Skandia International Symposium held during 1972 The subject should interest all physicians especially internists and cardiologists The contributors are well known in the field of cardiology The subjects discussed were important and numerous Among them for example were prevention, mortality vulnerability pathogenesis genetic predisposition, diabetes sudden death, and surgical care. As usual the discussions were interesting and provocative. The proceedings of this meeting follow the format of the proceedings of most meetings conducted throughout the world at present This is an important publication which contains a mass of interesting information.

Hemodynamic Stress and Relief of the Heart Edited by G Juznic, Basel, 1973 S Karger AG 183 pages Price $30 55

This book summarizes the proceedings of the Eighth European Congress on Ballistocardiography and Cardiovascular Dynamics Like the previous publication, this one contains a series of papers on cardiovascular dynamics with the use of ballistocardiography The papers are short but effectively describe the investigations of the various participants from many areas of the world, although mainly European. Even though ballistocardiography has been receiving less interest and attention in recent years, there are some investigators who are actively engaged in studying the BCC with the objective of applying it to clinical medicine This book also contains interesting historical presentations on the BCG This is a good publication which adequately summarizes the present state of ballistocardiography in medicine

Exercise Testing and Exercise Training in Coronary Heart Disease By John P Naughton, M D and Herman K Hellerstein, M.D New York, 1973 Academic Press, Inc 473 pp Price $16 00

This book summarizes the conference on "Exercise testing and exercise training in coronary heart disease" of 1973 The contributors varied widely in their interests and country of origin, most being from the United States Some of the contributors have published fundamental studies in this field, whereas others have not The curriculum is divided into three major sections namely (1) epidemiology physiology and biochemistry (2) psychology psychiatry and sociology and (3) cardiac rehabilitation. Several presentations are included in each section. Of course the emphasis is on man himself which is extremely important and welcomed.

This book presents a thorough review of the subject of exercise in coronary heart disease Some presentations are esoteric and will interest the practicing physician very little Nevertheless the book should interest all doctors

Book reviews

The Aortic Arch and Its Malformations—With Emphasis on the Angiographic Features Wade H Shuford, M.D., and Robert G Sybers, M D Springfield, Ill 1973 Charles C Thomas Publisher 264 pages. Price $19 75

This monograph on malformation of the aortic arch is a well organized and well illustrated presentation of anomalies of the thoracic aorta The authors have included a selected bibliography and excellent discussions of aortic arch anomalies with the intent of assisting practicing physicians, cardiologists vascular surgeons and radiologists The monograph includes discussions of the most common congen ital anomalies with emphasis on diagnosis and angiography This is a good book It is highly recommended to those physi cians involved with the management of cardiovascular dis eases

The Myocardial Cell for the Clinical Cardiologists Marianne L Legato, M D Mount Kisco N Y 1973 Futura Publishing Co 179 pages. Price $17 50

This book is primarily concerned with a review of the ultrastructure of the normal myocardial cell Legato clearly describes the general structure and morphology of organelles of the myocyte and sarcomeres of the heart. He presents the structures with emphasis on function and even as related to biochemical function The myocyte of the heart is the most important structure of the cardiac pump Its structure must be understood in order to know how it functions Legato has contributed a great deal to the field of electron microscopy with emphasis on the mammalian myocardium The illustra tions are very good and simple All cardiologists as well as everyone in cardiovascular research will find this to be a good book to have available for teaching and study

Cardiology Case Studies Nicholas P DePasquale M D and Michael S Bruno M D Flushing 1973 Medical Examina tion Publishing Co 300 pages. Price $10 00

This compendium of 55 cases of heart disease illustrates very nicely the importance of history taking bedside physi cal examination and simple laboratory studies in the diag nosis and management of heart disease Special procedures are employed when indicated. Although in Case 21 the authors used coronary arteriography in the clinical in vestigation and a normal arteriogram was found they failed to this reader s dismay to state clearly their diagnosis This might still reflect the inadequacies of the many special pro cedures introduced in clinical medicine This case merely re flects again the prevailing importance of bedside medicine The doctor must decide from his clinical knowledge and ex perience

The 55 cases are well presented the accompanying il lustrations comments and questions and answers are very good The cases are also well selected Physicians who read and study these case presentations will profit a great deal In fact the special procedures such as phonocardiogram carotid arteriogram and vectorcardiogram included in the case studies merely illustrate forcefully the lack of need for these as far as service to the patient is concerned. These only add to the exorbitant cost of medical care True they may be needed occasionally but rarely This is a good and interest ing publication

Biochemistry of Catecholamines Toshiharu Nagatsu, Baltimore 1973 University Park Press, 362 pages. Price $24 50

Although this book on the biochemistry of catecholamines will interest practicing physicians very little, it is an ex tremely important contribution to the medical literature. Nagatsu has summarized very effectively the biochemistry of substances which greatly influence the behavior of the heart and blood vessels. He discussed the sympathetic pathways of the catecholamines the biochemical action of these sub stances, and the action of inhibitors Assay methods are dis cussed along with a presentation of the problems related to assay methods In addition to biochemists this book should interest pharmacologists, physiologists, and investigators in cardiovascular fields. An extensive bibliography is included.

Valvular Heart Disease Edited by William Likoff M D and Albert N Brest, M D Philadelphia 1973 F A Davis Com pany 470 pages Price $15 00

This volume of Cardiovascular Clinics on Valvular Heart Disease is another valuable publication. Likoff the guest edi tor has gathered timely presentations related to valvular heart disease Diseases of the valves of man continue to plague people of the world Ideas regarding etiology preven tion medical and surgical management and diagnosis are among the main aspects of the presentation The role of echocardiography is included among the 17 papers of this publication The current status of valve replacement is well presented This is a very good member of the series of Car diovascular Clinics. The entire series is worth owning

Advanced Electrocardiography G L Lempert M D Brussels 1973 Verlag Gerhard Witzstrock GmbH 390 pages

Lempert has summarized the literature very briefly on electrocardiography He very briefly reviewed hundreds of publications and grouped them according to subject material such as lungs renal disease hypopotassemia diabetes heart, diseases of various organs and organ systems exercise tests and many others too numerous to list The references are clearly indicated so that the reader may refer to the original publications for details This publication is helpful for stu dents of electrocardiography The book condenses for the reader a large mass of publications from an extensive litera ture In fact the publications in the field of electrocardiogra phy are so numerous that it is impossible to read all the orig inal papers Lempert s book is a valuable review of recent publications in electrocardiography

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Editorial

Appraisal of digoxin bioavailability and pharmacokinetics in relation to cardiac therapy

John G Wagner Ph D
Ann Arbor Mich.

Butler and Chen[1] first reported on the preparation of digoxin specific antibodies Later Smith and associates[2,3] characterized the antibodies[2] and developed a radioimmunoassay for digoxin in serum or plasma[3] Subsequently it was shown that antibodies present in commercially available antiserum were not specific for digoxin but that digoxin digoxigen mono digitoxoside and digoxigen bis digitoxoside all reacted with the antibody to about the same degree[4,5] Digoxigenin also cross reacted, but to a much lesser degree[4,5] However earlier studies[6,7] indicated that all the metabolites of both digoxin and digitoxin are cardioactive to varying degrees in both the guinea pig and the cat. Only the aglycones appear to have greatly reduced activity in vivo Thus what low levels of metabolites one would measure by application of the radioimmunoassay would mostly be cardioactive Hence from a clinical point of view the radioimmunoassay procedure for digoxin is quite useful for monitoring individual patients determining therapeutic and toxic plasma or serum levels and in bioavailability studies where plasma or serum levels of digoxin and/or urinary excretion of digoxin are compared following administration of digoxin by *different routes* of administration (intravenously intramuscularly or orally) or as different commercially available dosage forms and specially made test formulations given by the oral route The specificity of the digoxin radioimmunoassay has been improved by a consideration of reaction rates as well as avidities of various species to bind to the antibody[8] Also various modifications of the radioimmunoassay procedure have been published.[5,9,10]

The label dose of digoxin which appears on the container of the dosage form which is administered to the patient is not the same as the *amount* of digoxin which reaches the circulation except when the drug is administered intravenously When digoxin is administered orally or intramuscularly an amount less than the label dose reaches the circulation. The ratio of the amount which reaches the circulation to the label dose varies both with the route of administration and the particular commercially available dosage form which is administered This bioavailability problem has been extensively studied recently[11-25] The bioavailability of digoxin has been assessed by two different methods (1) by comparison of the areas under the serum or plasma concentration curves in man (hereafter called the *area method*) and (2) by comparison of the relative amounts of digoxin excreted in the urine of man (hereafter called *urine method*) It is tenous to make interstudy comparison of results

From the Upjohn Center for Clinical Pharmacology The University of Michigan, Ann Arbor Mich

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Reprint requests to Dr John G Wagner Upjohn Center for Clinical Pharmacology The University of Michigan, Ann Arbor Mich. 48104

Books received

Current Therapy 1974 ***(Latest Approved Methods of Treatment for the Practicing Physician)*** Edited by Howard F Conn MD Philadelphia 1974 W B Saunders Company 914 pages

Cardiogenic Shock Mechanisms and Management Richard J Kones MD Mount Kisco N Y 1974 Futura Publishing Company 386 pages Price $22 95

Trace Elements in Human Nutrition Report of a WHO Expert Committee World Health Organization Technical Report Series No 532 65 pages Price $1 75

Bronchial Asthma Nicholas J Gross, MD PhD Hagerstown, Md 1974 Harper & Row Inc 74 pages. Price $3 95

The Heart ed. 3 J Willis Hurst MD Editor in Chief R. Bruce Logue MD Robert C Schlant MD and Nanette Kass Wenger MD editors New York 1974 McGraw Hill Book Company Inc 1833 pages

Medical Genetics Principles and Practice James J Nora and F Clarke Fraser Philadelphia 1974 Lea & Febiger Publishers 399 pages. Price $20 00

Respiratory Physiology—The Essentials John B West, MD PhD Baltimore 1973 The Williams & Wilkins Company 185 pages Price $6 95

Stroke Diagnosis and Management Current Procedures and Equipment William S Fields MD and John Moosy MD St Louis 1973 Warren H Green Inc 304 pages. Price $15 50

The Cure of Cancer and Heart Muscle Disease Dr Jules Samuels Amsterdam 1973 N V Cycloscoop Inc 227 pages

Bleeding Problems Diagnosis and Treatment Joseph A. Caprini MS MD Hagerstown Md 1973 Harper & Row Publishers Inc 62 pages Price $2 95

Preventive Medicine and Public Health Philip E. Sartwell, Englewood Cliffs, N J., 1973 Prentice Hall Inc., 1189 pages. Price $38 50

Announcements

International Congress on Electrocardiology

The First International Congress on Electrocardiology (Fifteenth International Symposium on Electro Vectorcardiography) will be held in Wiesbaden (West Germany) on Oct. 14 to 17 1974 (President Prof Dr Hubert Abel) For further information please address the Sekretariat of the Medical Clinic St Josefs Hospital 62 Wiesbaden (West Germany) Solmstrasse 15

area 0 to 8 hour under the serum concentration curve and between six day urinary excretion and first day urinary excretion of digoxin.

The above examples pertain to digoxin preparations available in the United States The bioavailability literature on digoxin is complicated since the Lanoxin tablets available in the United Kingdom are not the same as those available in the United States. In May 1972 Burroughs Wellcome & Co in the United Kingdom altered the production process for their Lanoxin tablets The absorption of the new English Lanoxin tablets was presented by the manufacturer as being about twice that of tablets produced before May 1972 This value of double the amount absorbed was supported by other investigators[15,20] However it appears that the bioavailability of the new United Kingdom Lanoxin tablets is very similar to that of the Lanoxin tablets which have been available in the United States to date

The rate of dissolution of digoxin from various commercial tablets in vitro has been correlated with bioavailability of digoxin in man as assessed by the area and urine methods[22,24] Since May 1972 all batches of Lanoxin tablets made in the United Kingdom have been subjected to a dissolution test to ensure consistently high dissolution rate[23] Extensive studies have also been carried out in the United States In the future it may be possible to exclude poorly performing digoxin tablets from the American market by establishing in vitro rate of dissolution specifications

When digoxin has been administered orally in the form of a hydroalcoholic solution (elixir) or in aqueous solution most investigators[21,22,24] have reported lower plasma or serum levels and per cent of dose excreted in the urine (hence lower bioavailabilities by the area and urine methods) than the known 100 per cent bioavailability attained by the intravenous route Some possible reasons for this are as follows (1) Part of the administered dose of digoxin is metabolized and the major part (about 80 per cent) is excreted unchanged in the urine[30] When digoxin is administered orally all of the drug ultimately absorbed passes via the portal vein to the liver where it is available to metabolizing enzymes. When the drug is administered intravenously only a portion of the blood reaches the liver on each circulation pass. This so-called "first pass effect"[31] following oral administration can account for some but not all of the reduced bioavailability of digoxin when it is presented in solution orally (2) There may be a "window effect" such that digoxin is only absorbed very rapidly from solution in the upper part of the gastrointestinal tract Hence part of the solution of digoxin after mixing with gastrointestinal contents passes the "window" due to gastrointestinal motility before it can be all absorbed (3) Intestinal tissue in the guinea pig and possibly in man can metabolically degrade digitalis glycosides[32] (4) Digoxin may have an unfavorable in vivo partition coefficient between the membrane and gastrointestinal fluids[33] (5) Acidic gastric juice (below pH 3) is capable of hydrolyzing digoxin[4]

Why do solid oral dosage forms such as tablets allow less digoxin to be absorbed than when the digoxin is administered orally as a solution? Most investigators have attributed this to the slow rate of dissolution of digoxin from tablets[14,17,20,23] Owing to the 'window effect' normal gastrointestinal travel rates are such that there is not enough time for all the digoxin to reach the solution state and become absorbed However this does not explain the results with all commercially available tablets With some tablets their construction and ingredients are such that some of the digoxin is "locked up" in the small particles produced after the tablet disintegrates Some digoxin apparently passes through the gastrointestinal tract in the solid state and never reaches the solution state Evidence for this phenomenon is that when such tablets are subjected to in vitro rate of dissolution tests only part of the label dose of digoxin is ultimately released even after the dissolution tests are run for long periods of time An example is digoxin tablets of Lot B_2 in Lindenbaum and associates'[12] study which gave very low plasma levels of digoxin When this lot was tested in vitro by Wagner and colleagues[2] it released in vitro an average of only 1 2 per cent of its digoxin content when stirred at 50 r p m in 500 ml of water at 37 C for two hours When the stirring rate was increased to 200 r p m. for an additional hour the tablets had released a total of only 3 6 per cent of their digoxin content By the normal official tablet assay procedure the digoxin content of these tablets could be determined. Hence the problem with this marketed Lot B_2 of Lindenbaum and associates[12] was not only that it was out of compliance with United States Phar

since investigators have used a wide variety of study conditions, such as the duration of the fasting period before and after the dose of digoxin, also they have varied the time interval of blood sampling and/or urine collection In addition some investigators have utilized normal human subjects and others have utilized cardiac patients In most studies single oral doses have been administered to normal human subjects and biological specimens have been assayed by the radioimmunoassay method In some studies multiple doses have been administered Some authors have compared peak plasma or serum concentrations of digoxin However, with digoxin although such comparisons may have clinical significance, the ratios of average peaks really do not reflect bioavailability of digoxin The more slowly absorbed preparations, such as tablets yield peak levels much lower than those obtained by the intravenous route and with rapidly absorbed preparations such as the elixir or aqueous solutions and the ratio of average peak for a tablet/average peak following intravenous will usually be lower than the corresponding ratio by the area method or urine method A consensus of the literature indicates that based on the area and/or urine methods the relative order of bioavailability of digoxin is as follows Rapid intravenous injection or infusion > sterile aqueous solution administered intramuscularly ≥ elixir or aqueous solution administered orally > Lanoxin tablets* administered orally > various other brands and *chemically equivalent* tablets available to date from other manufacturers Because of problems in interstudy comparisons it is difficult, if not impossible at present to assign a numerical value for bioavailability for each of the above However, some intrastudy results will be cited It should be noted that the reference in each study is assigned a value of 1 0 but the reference varies from study to study—being sometimes intravenous infusion sometimes the elixir administered orally and sometimes Lanoxin tablets administered orally

Based on calculation of 0 to 5 hour areas by the author from the data of Lindenbaum and associates,[12] tablets tested (and relative bioavailabilities) were as follows Lot A_1 (1 0) Lot B_1 (0 71), Lot B_2 (0 14), Lot C (0 28) Lot A_1 was Lanoxin, Lots B_1 and B_2 were manufactured by American Pharmaceutical Company and Lot C was manufactured by Davies Edwards

Only tablets of Lot B_2 in the Lindenbaum study failed to meet the U S P requirements for tablet to tablet variation in potency [26,27] The comments of Wagner and colleagues[22] pertaining to the article of Feldmann[28] were in relation to Lots A_1 and B_2 both of which passed U S P specification Thus the subsequent comments of Feldmann[29] seemed unnecessary

Based on calculation of 0 to 5 hour areas by the author from the data of Vieweg and Sode,[21] preparations tested at a 0 5 mg dose level and relative bioavailabilities were as follows Lanoxin pediatric elixir 0 05 mg per cubic centimeter (Lot 592B) (1 0) Lanoxin tablets 0 125 mg (Lot 880A) (0 81) individually wrapped Lanoxin tablets (Lot 048A) (0 78) and Lanoxin tablets 0 25 mg (Lot 377A) (0 64) Analysis of variance of the areas indicated that the bioavailability of the elixir was significantly greater than that of the tablets, but that the bioavailabilities of the three lots of tablets did not differ significantly This was only a four subject study The bioavailability of different strengths of Lanoxin tablets should be checked in a larger panel of subjects

Based on calculation of 0 to 96 hour areas Wagner and associates[22] reported average relative bioavailabilities in two normal subjects following 0 5 mg single doses as follows intravenous infusion (1 0) solution of digoxin in 5 per cent dextrose orally (0 80) Lanoxin tablets 0 25 mg (Lot 999A) (0 57), and digoxin tablets, 0 25 mg (Fougera & Co Inc Lot No 1510) (0 31) In a separate crossover study in eight normal subjects the Fougera tablets yielded average peak plasma levels and 0 to 96 hour areas under the plasma level curves which were only 59 and 55 per cent respectively of those attained with the Lanoxin tablets

Greenblatt and colleagues[25] administered single doses of 0 75 mg of digoxin Based on 0 to 8 hour areas and six day urinary excretion their data indicate the following relative bioavailabilities intravenous infusion (1 0) Lanoxin injection, intramuscularly (0 80 and 0 83) Lanoxin pediatric elixir 0 05 mg per cubic centimeter orally (0 67 and 0 65) Lanoxin tablets 0 25 mg orally (Lot 915E) (0 44 and 0 55) These authors[25] also reported highly significant correlations between six day urinary excretion of digoxin and

*Lanoxin tablets are manufactured by Burroughs Wellcome & Co U S A

area 0 to 8 hour under the serum concentration curve and between six day urinary excretion and first day urinary excretion of digoxin

The above examples pertain to digoxin preparations available in the United States The bioavailability literature on digoxin is complicated since the Lanoxin tablets available in the United Kingdom are not the same as those available in the United States In May 1972 Burroughs Wellcome & Co in the United Kingdom altered the production process for their Lanoxin tablets The absorption of the new English Lanoxin tablets was presented by the manufacturer as being about twice that of tablets produced before May 1972 This value of double the amount absorbed was supported by other investigators [15,20] However it appears that the bioavailability of the new United Kingdom Lanoxin tablets is very similar to that of the Lanoxin tablets which have been available in the United States to date

The rate of dissolution of digoxin from various commercial tablets in vitro has been correlated with bioavailability of digoxin in man as assessed by the area and urine methods [22 24] Since May 1972 all batches of Lanoxin tablets made in the United Kingdom have been subjected to a dissolution test to ensure consistently high dissolution rate [23] Extensive studies have also been carried out in the United States In the future it may be possible to exclude poorly performing digoxin tablets from the American market by establishing in vitro rate of dissolution specifications

When digoxin has been administered orally in the form of a hydroalcoholic solution (elixir) or in aqueous solution most investigators[21,22,24] have reported lower plasma or serum levels and per cent of dose excreted in the urine (hence lower bioavailabilities by the area and urine methods) than the known 100 per cent bioavailability attained by the intravenous route Some possible reasons for this are as follows (1) Part of the administered dose of digoxin is metabolized and the major part (about 80 per cent) is excreted unchanged in the urine.[30] When digoxin is administered orally all of the drug ultimately absorbed passes via the portal vein to the liver where it is available to metabolizing enzymes. When the drug is administered intravenously only a portion of the blood reaches the liver on each circulation pass This so-called first pass effect [31] following oral administration can account for some but not all of the reduced bioavailability of digoxin when it is presented in solution orally (2) There may be a window effect such that digoxin is only absorbed very rapidly from solution in the upper part of the gastrointestinal tract Hence part of the solution of digoxin after mixing with gastrointestinal contents passes the window due to gastrointestinal motility before it can be all absorbed (3) Intestinal tissue in the guinea pig and possibly in man can metabolically degrade digitalis glycosides [32] (4) Digoxin may have an unfavorable in vivo partition coefficient between the membrane and gastrointestinal fluids [33] (5) Acidic gastric juice (below pH 3) is capable of hydrolyzing digoxin [34]

Why do solid oral dosage forms such as tablets allow less digoxin to be absorbed than when the digoxin is administered orally as a solution? Most investigators have attributed this to the slow rate of dissolution of digoxin from tablets [14 17 20,23] Owing to the window effect" normal gastrointestinal travel rates are such that there is not enough time for all the digoxin to reach the solution state and become absorbed However this does not explain the results with all commercially available tablets With some tablets their construction and ingredients are such that some of the digoxin is locked up in the small particles produced after the tablet disintegrates Some digoxin apparently passes through the gastrointestinal tract in the solid state and never reaches the solution state. Evidence for this phenomenon is that when such tablets are subjected to in vitro rate of dissolution tests only part of the label dose of digoxin is ultimately released even after the dissolution tests are run for long periods of time An example is digoxin tablets of Lot B_2 in Lindenbaum and associates'[12] study which gave very low plasma levels of digoxin When this lot was tested in vitro by Wagner and colleagues[22] it released in vitro an average of only 1 2 per cent of its digoxin content when stirred at 50 r p m in 500 ml of water at 37 C for two hours. When the stirring rate was increased to 200 r p m. for an additional hour the tablets had released a total of only 3 6 per cent of their digoxin content By the normal official tablet assay procedure the digoxin content of these tablets could be determined. Hence the problem with this marketed Lot B_2 of Lindenbaum and associates[12] was not only that it was out of compliance with United States Phar

macopoeia specifications for tablet to tablet variation in potency[26] but also the tablet exhibited extremely poor dissolution characteristics[22] Only a small amount of the labeled dose was released in the in vitro dissolution test and a similar situation presumably existed in the gastrointestinal tract of man The particle size of the digoxin used in the preparation of digoxin tablets may also be a determinant of the bioavailability of digoxin Reduction of the particle size of digoxin used to prepare experimental tablets and capsules was shown to cause an increase in serum digoxin concentrations compared with results achieved with coarse digoxin particles which met the requirements of the British Pharmacopoeia[19] Such factors as the type and amount of disintegrating agent diluent and other excipients in the tablet with digoxin and the compressional force used to prepare the tablets can alter bioavailability of digoxin

Digoxin is 25 per cent bound to serum proteins and the remainder is free in solution in serum The portion protein bound is entirely bound to human serum albumin (HSA) The binding capacity of HSA is greatly in excess of therapeutic concentrations Under equilibrium conditions digoxin is reversibly bound to the red cell membrane and a simple washing procedure is sufficient to displace digoxin from the erythrocytes[35]

The elimination half life of digoxin in cardiac patients and subjects with normal renal function averages 1 5 to 1 7 days[18,36] Similar values are obtained from studies with tritiated digoxin[36] as those in which cold digoxin was administered and samples were assayed by the radioimmunoassay procedure[18] Such half lives were determined from terminal plasma concentration data—i e, enough time was allowed after dosing so that absorption was complete (if the drug was given orally) and distribution equilibrium had been attained (if the drug was given intravenously or orally) Following massive doses of digoxin shorter half lives of digoxin (10 to 20 hours) have been reported[37-40] but the data presented indicate that these ' half lives were estimated from plasma digoxin levels during the absorption distribution phase and are not comparable to the half lives as usually estimated Half lives estimated from plasma concentrations during the absorption distribution phase will always be less than the half life estimated from terminal plasma concentrations Thus there is no real evidence to date of any difference in the true elimination half life of digoxin following massive doses compared with therapeutic doses All one can really say from data published to date is that after massive doses of digoxin both the absorption and distribution phases are much longer than following therapeutic doses This explains some of the questions raised in a recent editorial[41]

Bloom and Nelp[42] showed that, within error, the renal clearance of tritiated digoxin is equal to the renal clearance of creatinine, and that the plasma half life of digoxin increased with decrease in the creatinine clearance Doherty and associates[43] reported serum digoxin half lives averaging 3 9 days (range 2 5 to 5 5 days) in eleven anephric patients They stated that in their experience anephric patients may be maintained on one half to two thirds of the usual dose of digoxin For patients with impaired renal function it has been shown that the elimination rate constant of digoxin K% (daily loss as per cent per day) is a linear function of endogenous creatinine clearance[44] The data of Jelliffe[45] gave the equation

$$K\% = 16\ 4 + 0\ 259\ Cl_{cr}$$

where Cl_{cr} is the endogenous creatinine clearance in milliliters per minute per 1 73 square meters of body surface area The data of Bloom and Nelp[42] gave the equation.

$$K\% = 20\ 0 + 0\ 173\ Cl_{cr}$$

The K% for patients with normal renal function is given by substituting $Cl_{cr} = 100$ into these equations, performing this operation gives normal K% values of 42 3 and 37 3 per cent per day respectively The elimination half life is then obtained by dividing the K% value into 69 3 the above normal K% values yield half lives of 1 6 and 1 9 days respectively For a patient with impaired renal function one substitutes the patient's Cl_c value into the equation and obtains a (K%) patient The patient maintenance dose is then calculated by the formula

$$\text{Patient maintenance dose} = \text{normal maintenance dose} \times \frac{(K\%)\ \text{patient}}{(K\%)\ \text{normal}}$$

Recently Reuning and colleagues[46] have presented evidence that the volume of distribution

of digoxin is lower in patients with impaired renal function than in subjects with normal function Steady state volumes of distribution (V_dSS) averaging 330 and 510 L respectively were reported Thus the steady state volume of distribution of patients with impaired renal function averages only 65 per cent of that of patients with normal renal function On the basis of this and other evidence these authors recommended that the loading dose of digoxin for patients with severely impaired renal function be decreased to one half to two thirds of the normal loading dose in order to achieve blood levels of digoxin in the desired therapeutic range

There are problems in applying simple linear pharmacokinetic models to digoxin Some of these are as follows (1) Plasma or serum digoxin concentrations plateau from about two to seven hours after cessation to an intravenous infusion[22] or following rapid intravenous injection of tritiated digoxin[47] Such a plateau is disregarded in simple linear compartment analysis (2) When radioactivity is measured following tritiated digoxin and when the radioimmunoassay procedure is used following cold digoxin some metabolites of digoxin are measured as well as unchanged drug[45] Pharmacokinetic modeling assumes measurement of only one species (3) Bile cycling of digoxin exists in man[36] and can cause secondary peaks on plasma digoxin concentration curves when patients eat soon after an oral dose.[20] Even in the absence of such visible evidence bile cycling still exists yet application of the simple two compartment open model ignores this (4) There is evidence of nonlinear tissue binding of digoxin[48] whereas the simple linear models assume linear binding Nonlinear binding would result in the ratio of tissue concentration/plasma concentration decreasing as the plasma concentration increases

Chiefly because of flexibility of route of administration and intermediate duration of action digoxin has become the digitalis glycoside predominatly used in hospitalized patients and, to a somewhat lesser extent, in office practice[49] Recent studies suggest that digoxin *per se* is still an excellent drug but that one must be much more careful in its use since new factors have come to the light *The Medical Letter*[50] recently published guidelines on the choice of a digoxin product and the author agrees with the statements therein Some quotations are digoxin tablets of poor bioavailability continue to be marketed and the practicing physician must be aware that under digitalization or toxicity may result from changes in source of lot of digoxin Switching back and forth between digoxin tablets from different manufacturers should not be encouraged at this time If the physician has any reason to question the effectiveness of a digoxin preparation serum digoxin concentrations should be measured in blood taken eight hours or more after the last oral dose (usual therapeutic serum range 0 5 to 2 0 *ng* per milliliter) many cardiologists advise that only Burroughs Wellcome digoxin (marketed in the United States as Lanoxin) should be used while awaiting industry wide establishment of dissolution rate standards by the FDA

When digitalizing patients by the intravenous route it must be remembered bioavailability of digoxin by this route is from 1 6 to 2 times that attained with Lanoxin tablets. Also no longer should doses given as Lanoxin pediatric elixir be exactly equated with doses given as Lanoxin tablets since the elixir provides higher peaks and areas for the same dose than the tablets

The author disagrees with Reuning and associates[16] that the loading dose of digoxin should be reduced in patients with severe renal failure and will publish the reason in the near future

Compliance is also a determinant of serum digoxin concentration[51] Formulas for establishing optimum digitalization based on age renal function and other factors do not apply to patients who do not take their medications Compliance cannot be ignored as a determinant of therapeutic response to digoxin Patients must be adequately counselled as to the importance of taking their medicine

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Clinical communications

A natural history study of the prognostic role of coronary arteriography

James F Brymer, M D
Thomas H Buter B A
Joseph A Walton Jr M D
Park W Willis III M D
Ann Arbor Mich.

As surgical operations are more widely applied in the treatment of coronary heart disease continued development of guidelines for the selection of patients for surgery is needed Operative mortality and morbidity rates remain significant in many centers The distribution and extent of coronary artery atherosclerosis and left ventricular function are thought to influence the surgical risk Knowledge of the influence of these factors on the outcome in patients managed medically is needed, so that operative risks and results can be seen in perspective and so that patients and physicians can compare the relative merits and expected outcome of medical and combined medical surgical treatment There are several recent contributions[1-5] reporting the natural history of arteriographically demonstrated and graded coronary occlusive disease Few of the series are large however and only two reflect a follow up of five years or more [1,5] The object of the present report is to add to the gradually accumulating body of data in this area. Record of patients who underwent coronary arteriography at the University of Michigan teaching hospitals were collected and the natural history of their disease to date is presented with emphasis on the prognostic value of the knowledge of the extent of lesions the presence of prior myocardial infarction and the effect of left ventricular dysfunction

From the Section of Cardiology Department of Internal Medicine University of Michigan Medical Center Ann Arbor Mich

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Reprint requests to Park W Willis, III, M D Director Section of Cardiology University of Michigan Medical Cent Ann Arbor Mich. 48104

Materials and methods

Coronary cinearteriograms and clinical records of 175 patients studied at the University of Michigan Hospital and the Ann Arbor Veterans Administration Hospital from January 1965 through June 1972 were reviewed The 129 patients studied at Wayne County General Hospital Eloise Mich between July 1968 and December 1970 were subsequently added to the review The 1970 cut off date was used in the latter group to assure at least two years follow up in those patients. All studies that were technically inadequate to allow grading of all major coronary branches were excluded Also excluded were patients with valvular or primarily muscular heart disease

An attempt was made to correlate the character of clinical symptoms with the arteriographic appearance of the coronary arteries Angina pectoris was strictly defined (Table I) as visceral pain involving at least some part of the sternum precipitated by effort, emotion cold exposure or heavy meals lasting not longer than 20 minutes after cessation of activity and usually promptly relieved by nitroglycerin Pain syndromes that did not meet all these criteria were called atypical We did not attempt to subdivide the atypical syndromes because often the recorded histories were not sufficiently detailed to allow precise distinction between probable cardiac and noncardiac pain A few patients were included who did not complain of pain but had other evidence—usually an abnormal electrocar

Table I Criteria used to identify typical angina pectoris

1. Must involve some part of the sternum
2. Must be precipitated by exertion emotion cold exposure heavy meals
3. Must be visceral pain—i e squeezing burning tightness
4. Must not last longer than 20 minutes after cessation of activity
5. Should be relieved promptly by nitroglycerin

Table II Arteriographic scoring system*

Points	*Degree of obstruction*
0	*No abnormality seen*
1	Trivial irregularity in lumen diameter
2	Localized area of narrowing—greater than 50 per cent less than 90 per cent
3	Multiple areas of narrowing in the same vessel—50 to 90 per cent
4	Narrowing greater than 90 per cent
5	Complete obstruction

After Friesinger and associates [1]

Table III *Comparison of clinical symptoms with arteriogram score*

	Score			
	*0 3**	*2 5†*	*6 10*	*11 15*
No chest pain	2	1	7	2
Typical angina pectoris‡	14	23	88	51
Atypical chest pain‡	79	12	18	6

No more than a one point lesion in any vessel
†At least a two point lesion in one vessel
‡False positives eight per cent (typical angina pectoris with normal arteriogram) false negatives 31 per cent (atypical pain with abnormal arteriogram)

diogram (ECG)—suggesting coronary disease

Coronary cinearteriograms were scored according to the method described by Friesinger Page and Ross[1] (Table II) The right coronary artery (RCA), the left anterior descending (LAD) and left posterior circumflex (LPC) branches were scored individually and the scores added to arrive at the total score for each patient The maximum possible score thus was 15 points Lesions of the main left coronary artery were treated as if both LAD and LPC were involved

Left ventricular cineangiocardiograms were reviewed and graded when these were available Prior myocardial infarction was diagnosed only when diagnostic QRS changes were present in an electrocardiogram recorded prior to cardiac catheterization

Follow up information on the patients was obtained from the hospital records of those patients who attended the cardiac clinic of the participating hospital The referring physicians of those patients who did not return were contacted by telephone and in some cases the patients were contacted personally by mail or telephone

Results

A total of 304 patients was included in the review 251 were men (ages 18 to 69, median 47) and 53 were women (ages 28 to 66 median 46)

The patients presenting symptoms were compared with arteriographic scores Close correlation was found between typical angina pectoris and serious coronary obstruction by the arteriogram Ninety two per cent of the patients with typical angina had at least a two point lesion (greater than 50 per cent obstruction) in at least one major vessel Atypical pain was much less specific 31 per cent of such patients had evidence of serious disease and 69 per cent had normal appearing arteriograms of minor obstruction (less than 50 per cent occluded) in one or more vessels Nonspecificity in the latter group was probably related to the wide range of presenting complaints included in the atypical category (Table III)

Eighty five patients subsequently underwent an operative procedure for coronary heart disease (Vineberg mammary artery implant or saphenous vein aortocoronary bypass grafts) and are not considered further

Ninety five patients had relatively normal appearing coronary arteriograms Two of these 95 patients died during the follow up period (2 per cent) Mean follow up interval for this group of patients was 24 months One of the patients who died was a 28 year old black hypertensive woman who had had repeated episodes of ventricular paroxysmal tachycardia in the hospital The arrhythmia was associated with bouts of

chest pain usually occurring at rest eventually controlled by bretylium tosylate and she was maintained on that drug as an outpatient Her coronary arteries appeared completely normal She died suddenly at home several months following her study Aside from the arrhythmia her ECG had been normal as was her left ventriculogram The other patient who died was one of seven patients with relatively normal appearing coronary arteriograms but ECG evidence of prior myocardial infarction. She was a 56 year old white woman whose precatheterization ECG showed QRS changes of old anterior myocardial infarction Nevertheless her coronary arteriogram was completely normal She was brought to the hospital dead on arrival after she collapsed suddenly at home two days following her arteriography

There remained a nonoperative group of 124 patients with abnormal coronary arteriograms For the purposes of this report of natural history only survival of the patients was considered The follow up period ranged from just a few months to nearly seven years with a mean follow up of 19 months Of these 124 patients, 21 (17 per cent) died during the follow up period Five per cent of these patients have been lost to follow up

Among those with mild to moderately severe disease (2 to 7 points) the mortality rate was 11 per cent (6 of 57) 22 per cent (15 of 67) of those with severe disease (8 to 15 points) died Among those with single vessel disease the mortality rate was 10 per cent (4 of 41) with two and three vessel disease it was 20 per cent (9 of 44) and 21 per cent (8 of 39) respectively

It became apparent that left anterior descending disease was highly prevalent in those who died. Nineteen of 21 (90 per cent) patients who died had significant LAD disease With the data arranged to reflect the influence of LAD involvement, the mortality rate was doubled—14 per cent (4 of 28) vs. 7 per cent (2 of 29)—in the mild to moderate disease group (two to 7 point score) when LAD was involved. Among the severe disease patients (8 to 15 points) the mortality rate was nil (none of 13 patients) when LAD was not significantly involved (despite the presence of severe disease in the other major coronary branches) This difference is not statistically significant (p = 0 08)

Using the standard life table methods[9] Figs 1 and 2 were derived to demonstrate survival results graphically The latter portion of each curve tends to flatten because of the small number of patients at the later points of follow up and probably does not accurately reflect prognosis This applies both to the diagram illustrating survival by total score (Fig 1) and to Fig 2 which illustrates the prognosis for normal subjects and for those with one two and three vessel disease

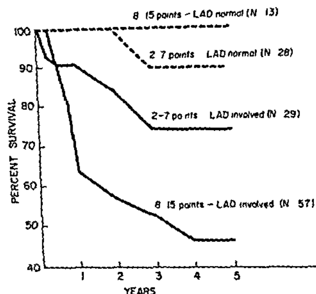


Fig 1 Survival of nonoperative patients grouped by arteriographic score Whether LAD was involved is indicated

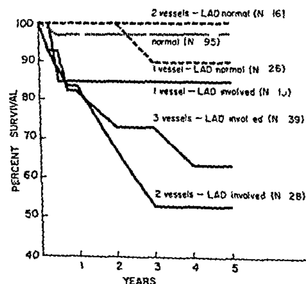


Fig 2 Survival of nonoperative patients grouped by number of vessels seriously involved When LAD was involved, this is indicated Survival of normal subjects is also shown.

Seventeen patients had left main coronary artery lesions of greater than 50 per cent occlusion and eight of these (47 per cent) died within one to 23 months

Other factors that might influence the outlook in these patients were considered Those patients with prior history of myocardial infarction and ECG evidence of diagnostic QRS changes incurred a mortality rate of 21 per cent, those without definite evidence of infarction had a mortality rate of only eight per cent Similarly, and perhaps as an effect of prior infarction, left ventricular dysfunction by cineangiocardiogram was associated with a 26 per cent mortality rate regardless of the degree of coronary artery obstruction, whereas only four per cent of those with apparently normal left ventricular function died Left ventriculograms were available for review in 90 per cent (111 of 124) of these cases

Discussion

In this series of patients we found close correlation of typical angina pectoris when strictly defined with arteriographic evidence of serious (greater than 50 per cent) coronary obstruction Our finding of 92 per cent positive correlation is consistent with previously reported results [1 6]

We found that 98 per cent of patients with normal or less than 50 per cent obstructed coronary arteries survived through the follow up period This finding that normal arteriograms imply a good prognosis regardless of the severity or variety of clinical symptoms is in agreement with recent reports [1 7 8] Similarly, we found evidence confirming other reports[1 5] indicating that survival of patients with coronary artery disease treated medically or observed without treatment varies directly with the severity of the disease the number of vessels involved the presence of prior myocardial infarction and left ventricular dysfunction

We found that serious disease in the left anterior descending branch implied over all a worse prognosis than a normal appearing LAD—whether it was the only vessel involved or even more strikingly when LAD was involved in combination with disease in other vessels This difference approached statistical significance when the coronary occlusions were high grade (8 to 15 point scores by the system used) even though numbers of patients are small and follow up relatively short. We feel that, although it has been mentioned by others [5] the particular influence on the mortality rate of LAD disease has been insufficiently stressed

We conclude from these data that those factors which appear to adversely affect survival in surgically treated patients—namely, severe multiple vessel disease, particularly left main or anterior descending coronary artery disease and left ventricular dysfunction—play a similar role in patients managed medically or observed without treatment Conversely, mild coronary disease the absence of demonstrable prior myocardial infarction and normal left ventricular contraction a combination of factors thought to characterize the ideal operative candidate appear also to portend a low mortality rate and favorable outcome when an operation is not performed

It remains for continued follow up of groups of patients such as ours and of similarly well documented and followed groups of patients having coronary operations to demonstrate differences between the groups and answer the question whether the results of operative therapy justify the risks and expense of that mode of treatment.

Summary

Coronary cinearteriograms clinical records and left ventriculograms of 304 patients studied for evaluation of chest pain were reviewed Clinical and follow up data on survival of the normal subjects and the nonoperative group with abnormal arteriograms are presented

Ninety two per cent of patients with typical angina pectoris had serious coronary occlusive disease Ninety eight per cent of patients with relatively normal coronary arteriograms survived for one to 60 or more months (mean follow up period 24 months)

There was a high mortality rate when the left main coronary artery was involved (47 per cent) and when the left coronary anterior descending branch was seriously occluded (28 per cent when arteriographic scores were high and 14 per cent when total scores were low) and a low mortality rate (0 to 7 per cent) when the LAD was normal Mean follow up interval in these groups was 19 months

The mortality rate was nearly three times greater when patients had QRS changes on ECG

of prior myocardial infarction and six times greater when left ventricular contraction was significantly impaired.

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Use of phentolamine in acute myocardial infarction

Lawrence Gould M D
C V R Reddy, M D
Paul Kalanithi, M D
Luis Espina, M D
Robert F Gomprecht, M D
Bronx and New York, N Y

The systemic arterial pressure is *frequently* elevated *during the course* of an acute myocardial infarction, probably due to the release of catecholamines from the heart [1] A reduction of the elevated blood pressure by decreasing the myocardial oxygen consumption requirements, should limit the extent of the infarct and improve cardiac performance [2] Based on these concepts nitroglycerine [3] nitroprusside [4] and phentolamine[5] have been administered to patients with an acute myocardial infarction A reduction of the elevated systemic arterial pressure has led to a fall in the left ventricular end diastolic pressure and a rise in the cardiac output.

If a reduction in the myocardial oxygen consumption requirements is the key factor in limiting the extent of the myocardial infarction, then a decrease in the blood pressure irrespective of its initial level, should be beneficial In order to evaluate this concept we have used phentolamine to decrease the normal or low blood pressure in patients with an acute myocardial infarction and left ventricular dysfunction

Methods

Studies were performed within the first 24 hours after the onset of symptoms in 10 patients who had acute transmural myocardial infarction documented by a typical history electrocardiographic findings and serum enzyme changes Seven patients were males and three patients were females The average age of the group was 60 years Most of the patients had received therapy, when needed in the form of oxygen narcotics sedatives diuretics, and lidocaine before the study The procedure was carefully explained to the patient and informed consent was obtained

Right heart catheterization was performed using a Swan Ganz flow directed balloon type catheter inserted through the right antecubital vein Arterial pressure was measured through a Cournand needle in the brachial artery Pressures were measured using Statham transducers and recorded with the electrocardiogram on an Electronics for Medicine DR12 machine The left ventricular filling pressure was taken as the mean of the pulmonary capillary wedge pressure Mixed venous blood was obtained from the pulmonary artery and arterial blood from the brachial artery Arterial and mixed venous oxygen contents were determined by the method of Van Slyke and Neill Oxygen consumption was not determined because the spirometer was too large to fit near the patient s bed in the coronary care unit Therefore the cardiac output was determined by the Fick technique utilizing an oxygen consumption of 130 c.c per minute per square meter for each patient It is known that an infusion of phentolamine does not statistically change the oxygen consumption [6 7]

After recording the control hemodynamic measurements phentolamine was infused for 30 minutes at a dose of 0 4 mg per minute The cardiac pressures and blood for the arteriovenous

From the Department of Medicine Misericordia Fordham Affiliation Bronx and New York Medical College New York

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Reprint requests to Lawrence Gould M D Department of Medicine Misericordia Fordham Affiliation Bronx N Y 10466

oxygen difference were obtained at the conclusion of the infusion

Calculations The systolic ejection time in milliseconds was measured from the beginning of the upstroke to the dicrotic notch of the arterial pressure recorded at 100 mm. per second. The tension time index per minute in millimeters of mercury per second per minute is the product of the heart rate mean systolic arterial pressure and systolic ejection time The systemic vascular resistance in dynes sec cm $^{-5}$ was calculated from the formula mean arterial pressure × 1 332/cardiac output (milliliters per second)

The statistical significance of the difference (P value) between the control values and the phentolamine values were calculated with the paired t test.

Results

Complete data on all 10 patients are presented in Table I In addition the average values before and after the phentolamine infusion are listed in Table II with the statistical analysis

As a result of the phentolamine infusion the average cardiac index increased from 2 44 to 3 58 L/min./M ^{2} ($p < 0.02$) while the stroke index increased from 26 to 34 ml /beat/M ^{2} ($p < 0.05$) The arteriovenous oxygen difference decreased from 5 5 to 3 8 volumes per cent ($p < 0.01$) The left ventricular filling pressure fell in every patient from a mean of 21 mm Hg in the control period to 13 mm. Hg during the phentolamine infusion ($p < 0.001$) Similarly the right ventricular filling pressure decreased in every patient from a control value of 10 mm Hg to a treatment value of 7 mm Hg ($p < 0.001$) Phentolamine decreased the arterial pressure from a mean of 86 to 76 mm. Hg ($p < 0.001$) and the systemic peripheral resistance from a control of 1 627 to 952 dynes sec cm $^{-5}$ ($p < 0.02$) The tension time index per minute was minimally increased after the phentolamine infusion

Discussion

The present study revealed that phentolamine administration produced, in the patients with a recent myocardial infarction a significant reduction in the left ventricular filling pressure and an elevation in the cardiac index. This improvement in cardiac function was accomplished with only a minimal reduction in the systemic arterial pressure irrespective of its initial level Indeed, nine of the 10 patients had either a normal or a low presenting blood pressure

Kelly and co workers[5] had also observed that hemodynamic improvement could be achieved with a phentolamine infusion in patients with hypertension associated with an acute myocardial infarction It had previously been demonstrated that an infusion of phentolamine is an effective treatment of congestive heart failure[6-8, 9] or pulmonary edema[10] in patients without an acute myocardial infarction

This improvement in cardiac function may be explained by the recent observations of various workers Dairman and co workers[11] administered phentolamine (5 mg per kilogram) to rats At the height of alpha receptor blockade the conversion of a tracer dose of tyrosine ^{14}C to norepinephrine in the heart brain and adrenal gland was increased threefold with no alteration in specific activity of tyrosine in blood and tissues From these studies Dairman and co workers concluded that receptor blockage led to increased synthesis and release of norepinephrine in the three organs that were measured. This contention has received support from the recent work of Bagwell and co workers[12] They administered 5 mg per kilogram of phentolamine to seven experimental animals and observed an increase in the left ventricular contractile force If the animals were pretreated with reserpine the inotropic action of phentolamine could be blocked. A subsequent infusion of norepinephrine could then restore the inotropic effect The authors concluded that the positive inotropic action of phentolamine is indirect and dependent on the release of norepinephrine

It has recently been demonstrated that phentolamine has beta adrenergic stimulating properties as well as alpha adrenergic blocking effects This beta adrenergic stimulating action is suggested by the observation that the fall in blood pressure and the increase in cardiac rate produced by 5 mg of phentolamine can be significantly blocked by the prior administration of propranolol[13] Propranolol can similarly block the inotropic and chronotropic action of phentolamine in dogs.[14]

Phentolamine is known to be an alpha adrenergic blocking agent. This is based on the observation that it can antagonize or even reverse the pressor response to epinephrine[15-17]

Table I Complete hemodynamic data on ten patients

Patient No and condition	*Experimental state—control and phentolamine*	*Sex/age*	*R.A (mean mm. Hg)*	*R.V S/D (mm. Hg)*	*P.A S/D (mm. Hg)*	*P.A. (mean, mm. Hg)*
1 Anterior wall myocardial infarction		M/55	12	60/12	60/28	39
			8	50/ 8	50/22	32
2 Anterior wall myocardial infarction		F/54	13	30/13	30/23	25
			9	22/9	22/15	17
3 Anterior wall myocardial infarction		M/56	23	60/23	60/35	43
			17	56/17	56/27	37
4 Anterior wall myocardial infarction		F/42	3	25/3	25/12	16
			0	12/0	12/6	8
5 Anterior wall myocardial infarction		M/83	0	18/0	18/9	12
			0	9/0	9/5	6
6 Inferior wall myocardial infarction		M/62	9	40/9	40/27	31
			6	25/6	25/17	19
7 Anterior wall myocardial infarction		M/72	10	40/10	40/23	28
			7	23/7	23/15	18
8 Lateral wall myocardial infarction		M/25	10	32/10	32/18	23
			7	18/7	18/12	14
9 Inferior wall myocardial infarction		F/81	14	50/14	50/33	39
			9	36/9	36/18	24
10 Inferior wall myocardial infarction		M/72	10	32/10	32/17	22
			7	23/7	23/14	17

Table II Average changes of hemodynamic parameters before and after phentolamine

	Control	*Phentolamine*	*P value*
Stroke index (ml /beat/M^2)	26 ± 9 0	34 ± 9 8	< 0 05
Systemic peripheral resistance (dynes sec cm^5)	1 627 ± 639	952 ± 210	< 0 02
Brachial artery mean pressure (mm Hg)	86 ± 16 3	76 ± 14 4	< 0 001
Pulmonary artery mean pressure (mm Hg)	28 ± 9 7	19 ± 8 2	< 0 001
Arteriovenous oxygen difference (vol %)	5 5 ± 1 4	3 8 ± 1 0	< 0 01
Cardiac index (L /min /M^2)	2 44 ± 0 49	3 58 ± 1 20	< 0 02
Pulse rate (beats/min)	97 ± 17 8	109 ± 19 7	< 0 001
Tension time index per minute (mm Hg/sec /min)	2 654 ± 838	2 779 ± 915	< N.S
Right atrial mean pressure	10 ± 5 8	7 ± 4 6	< 0 001
Pulmonary wedge mean pressure (mm Hg)	21 ± 8 7	13 ± 6 4	< 0 001

Mean ± S D

The blockage thus produced is relatively transient A mild sympatholytic action becomes manifest only with the use of very large amounts of this agent [18] The drug also has a peripheral vasodilating effect which is not blocked by atropine [19] The drug s relatively weak sympathetic blocking action as well as its antagonism to the circulatory catecholamines cannot adequately explain the striking vasodilation that results from its use under normal resting conditions Taylor and co workers[20] believe that a direct relaxing effect on the vascular smooth muscle plays the dominant role in the production of the conspicuous peripheral vasodilation However the recently described beta adrenergic stimulating action of phentolamine probably also contributes to the peripheral vasodilation

The various factors that affect myocardial oxygen consumption have recently been delineated. [1] The increased velocity of contraction and

Wedge (mean, mm. Hg)	B.A. S.D. (mm. Hg)	B.A. (mean, mm. Hg)	Rate (beats/minute)	$A-VO_2$ difference (Vol. %)	C.I. (L./min./M^2)	S.I. (ml./beat M^2)	Peripheral Resistance (dynes sec. cm^{-5})	TTI/min. (mm. Hg/sec./min.)
26	120/68	85	97	5.0	2.61	27	1 300	2 560
21	100/52	68	103	4.3	2.96	29	915	2 270
15	98/70	80	72	3.8	3.27	45	1 240	1 980
11	95/55	69	88	3.0	4.16	47	850	2 340
35	165/100	122	105	—	—	—	—	4 500
25	154/90	111	125	—	—	—	—	5 180
13	108/75	86	115	4.9	2.55	26	1 620	2 270
4	90/60	70	130	2.9	4.32	33	770	2 340
5	130/60	83	70	4.6	2.71	39	1 380	2 550
3	120/60	80	75	3.9	3.21	43	1 130	2 520
26	80/58	66	115	5.1	2.55	22	1 160	1 330
13	70/50	56	124	4.7	2.77	23	820	1 740
25	80/57	65	100	6.5	2.00	20	1 370	2 080
17	75/55	62	115	5.0	2.60	23	1 010	2 240
20	120/78	95	125	4.7	2.76	22	1 620	3 300
14	115/70	85	138	2.0	6.49	47	610	3 500
30	170/70	104	79	8.8	1.48	15	3 380	3 360
14	130/55	80	88	3.8	3.41	39	1 110	2 860
13	110/60	77	95	6.3	2.06	22	1 570	610
10	105/60	75	107	5.0	2.32	22	1 350	2 800

the improvement in contractility produced by phentolamine[6] would be associated with an increase in the myocardial oxygen consumption. The tension time index per minute which is a hemodynamic determinant of myocardial oxygen consumption rose only minimally in our patients after phentolamine administration. The intramyocardial tension as defined by the law of La Place plays a major role in the oxygen requirements of the heart. It has previously been demonstrated that the left ventricular end diastolic volume is reduced in patients with cardiac disease after a phentolamine infusion.[8] Thus this reduction in cardiac size would lead to a diminution in the myocardial oxygen consumption requirements. Recently Chatterjee and co workers[22] administered phentolamine to patients with an acute myocardial infarction. They observed that the myocardial oxygen consumption fell after the phentolamine infusion.

There are now very interesting efforts at this time to limit the extent of tissue damage during acute myocardial infarction by means of a wide variety of agents and interventions. These approaches to therapy include hypotensive drugs, intra aortic balloon pumping, mannitol and drugs like nitroglycerin which decrease cardiac filling.

In order to evaluate the effects of pharmacologic and hemodynamic interventions in acute myocardial infarction one can even employ noninvasive techniques. Precordial S-T segment elevation mapping can delineate the extent of ischemic injury.[23] The introduction of a drug which limits the extent of ischemic injury should produce a reduction in the ST segment elevations.

Nitroprusside[4] and nitroglycerine[5] have been used in the therapy of an acute myocardial infarction with an improvement in left ventricular performance. However these agents have no primary inotropic activity. Since phentolamine has a positive inotropic action, a marked reduction in the systemic pressure of a normotensive or a hypotensive patient is not required to improve cardiac performance. The other commonly used drugs to eliminate signs of congestion in acute myocardial infarction are digitalis and diuretics. Digitalis has not been found to effectively improve left ventricular function in the early stages of a myocardial infarction.[24] The diuretics can reduce the intravascular volume to such a degree

that a fall in the cardiac output and systemic pressure can result[25]

Phentolamine can improve hemodynamic performance in patients with a recent myocardial infarction by virtue of vasodilation and positive inotropy If the cardiac output is reduced the positive inotropic action of the drug would be particularly beneficial It now seems advisable to widen the clinical experience with this drug

Summary

Right sided cardiac pressures were obtained with a Swan Ganz catheter in 10 patients within the first 24 hours after a myocardial infarction Brachial artery pressures were obtained with a Cournand needle Cardiac pressures and arteriovenous oxygen differences were obtained before and immediately after the 30 minute infusion of phentolamine administered at 0 4 mg per minute Seven patients were normotensive 2 were hypotensive and 1 was hypertensive With phentolamine, all of the patients demonstrated a significant decrease in the right and left ventricular filling pressures, a rise in the cardiac index, and a small decrease in the arterial pressure Phentolamine can greatly improve cardiac function in acute myocardial infarction, regardless of the level of the initial blood pressure

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Left ventricular hemodynamics and contractile pattern after aortocoronary bypass surgery

Factors affecting reversibility of abnormal left ventricular function

Robert I Hamby M D
Farouk Tabrah M D
Agop Aintablian M D
Marvin L. Hartstein M D
B George Wisoff M D
New Hyde Park and Stony Brook N Y

The introduction of aortocoronary bypass surgery permitted a new approach to the management of patients with angina pectoris Clinical studies indicate that complete relief of symptoms can be expected in the majority of patients undergoing such a surgical procedure [1-5] Hemodynamic abnormalities and localized disorders of left ventricular contraction are commonly present in patients with symptomatic coronary artery disease [6-9] Intra operative[10,11] and post operative[12,13] studies have indicated that left ventricular performance may improve as a result of aortocoronary bypass surgery Furthermore in many patients abnormal contractile patterns of the left ventricle improve or disappear after surgery This report will describe our experience in a large group of patients undergoing aortocoronary bypass surgery with all grafts patent in the postoperative study The purpose of the present communication is to define the optimal changes in left ventricular hemodynamics and myocardial wall changes that may be anticipated after successful aortocoronary bypass surgery Thus only patients who demonstrated patency of all grafts placed at the time of surgery were selected Furthermore the changes noted postoperatively will be related to the number of grafts placed at the time of surgery Preoperative variables will be evaluated which may assist in predicting which patients will have complete reversal of left ventricular wall abnormalities as a result of coronary bypass surgery

Patients and methods

Selection of patients Patients with angina pectoris were studied both before and two to four weeks after aortocoronary bypass surgery Based on preoperative evaluation of the selective coronary angiograms bypass vein grafts were performed on all vessels considered operable by the surgeon with saphenous vein autograft and extracorporeal support Patients with an ejection fraction of less than 0 30 were not accepted for surgery Satisfaction of the following criteria was necessary to include a patient in this study Postoperative studies had to demonstrate patency of all grafts placed at the time of surgery with good run off Preoperative and postoperative left ventricular angiograms had to be technically satisfactory for evaluation of left ventricular wall motion and volume studies We excluded patients who also had valve replacement infarctectomy or aneurysmectomy at the time of coronary bypass surgery A total of 104 patients met the criteria for inclusion They were divided in three groups according to the number of grafts placed at the time of surgery (Table I) Group I consisted of 47 patients with single grafts and included 33

From the Department of Medicine Cardiology Division and the Department of Surgery Cardiovascular Division Long Island Jewish Hillside Medical Center New Hyde Park N Y Queens Hospital Center Affiliation Jamaica N Y and School of Medicine Health Sciences Center State University of New York at Stony Brook Stony Brook N Y

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Reprint requests Dr Robert I Hamby Long Island Jewish Hillside Medical Center New Hyde Park N Y 11040

Table I Clinical background and bypass flow of patient series

	Group I Single grafts		Group II Double grafts	Group III Triple grafts
	IA LAD	IB RCA		
Number of patients	33	14	47	10
Age (yrs)				
Mean ± 1 SD	52 ± 10.4	56 ± 9.0	53 ± 8.3	52 ± 5.5
Range	33-74	32-66	34-72	45-62
Sex, M/F	28/5	11/3	44/3	10/0
Duration of angina (yrs)				
Mean ± 1 SD	1.5 ± 1.7	1.7 ± 1.4	2.4 ± 2.0	4.1 ± 3.6
Angina pectoris				
Class III or IV	16	8	30	6
Unstable angina	17	6	17	4
Myocardial infarction (by ECG)	3	5	14	3

patients (Group IA) with single grafts to the left anterior descending artery and 14 patients (Group IB) with grafts to the right coronary artery. Group II consisted of 47 patients with a double vein bypass procedure. All but two of these patients had one of their grafts to the left anterior descending artery, while 33 patients had grafts to the right coronary artery and sixteen patients had grafts to the circumflex artery. Group III consisted of ten patients with triple vein bypass grafts. The functional classification of these patients was based on the New York Heart Association criteria.[19] Unstable angina pectoris was defined as multiple episodes of anginal pain occurring at rest, lasting over ten minutes, *only temporarily* relieved by nitroglycerin, and associated with transient ST and/or T wave changes in the electrocardiogram (ECG). Patients diagnosed as having unstable angina were operated on the same day as the preoperative study. A history of prior myocardial infarction was accepted only if documented by the referring doctor. The ECG diagnosis of a myocardial infarction was based on accepted criteria.[20]

Methods

All studies were performed after drugs (i.e., anti-arrhythmic drugs, digitalis and propranolol) were *discontinued* for at least three days. Preoperative studies consisted of right and trans-septal combined with retrograde left heart catheterization. The normal left ventricular end-diastolic pressure for this laboratory is 11 mm Hg or less. Left ventricular angiograms were obtained by injecting *0.50 to 0.75 ml* per kilogram of 90 per cent sodium meglumine diatrizoate into the left ventricle through the trans-septal catheter while recording left ventricular pressure through the retrograde catheter. Cineangiograms were taken with a 35 mm camera at 60 frames per second while recording the left ventricular pressure and ECG on the cine film (Cinetrace, Electronics for Medicine) and on photographic paper. In many patients, after the completion of the injection of contrast material the *trans-septal catheter was promptly withdrawn* so as to avoid ventricular premature beats. When the left ventricular angiogram was completed, a grid of known dimensions was positioned at the approximate location of the left ventricle and filmed to permit correction due to magnification. After completion of the left ventricular angiogram, selective coronary angiograms were performed in multiple projections, using methods described by Sones and Shirey[21] or Judkins.[22] Postoperative studies were performed in the same cardiac catheterization laboratory as the preoperative studies utilizing a percutaneous transfemoral approach for both the left ventricular and selective saphenous vein angiograms. The left ventricular angiograms were performed,

Table II Preoperative and postoperative hemodynamics in Group I patients (single bypass)

	A *LAD bypass* 33		*p*	*B* *RCA bypass* 14	
No. of patients	*Preoperative*	*Postoperative*		*Preoperative*	*Postoperative*
Heart rate	81 ± 13	96 ± 11	<0 001	83 ± 17	96 ± 19
Left ventricular					
End diastolic pressure (mm. Hg)	11 ± 5 5	9 ± 3 4		10 ± 3 7	9 ± 4 0
End diastolic volume (ml./M.²)	66 ± 14	64 ± 13		67 ± 21	69 ± 16
Stroke volume (ml./M.²)	44 ± 8	45 ± 7		41 ± 7	44 ± 9
Ejection fraction	0 68 ± 0 07	0 71 ± 0 05		0 62 ± 0 09	0 63 ± 0 11
Stroke work (Gm m./bt./M.²)	70 ± 20	70 ± 17		75 ± 17	72 ± 21

utilizing the same technique (40 degree right anterior oblique projection) as the preoperative study while the ECG was recorded simultaneously on the cine film. Left ventricular volumes were obtained, using the area length method[23] and the regression equation derived by Hermann and Bartle.[24] The left ventricular end diastolic volume index and ejection fraction determined in 25 patients with normal left ventricles using this method was 69 ± 21 ml per square meter and 0 66 ± 0 12 respectively The cine films were projected with a 35 mm. projector (Vanguard Instrument Corporation) on a ground-glass screen For the determination of left ventricular volumes and contractile pattern only normal sinus beats were utilized if not preceded by a ventricular premature beat. The area of the left ventricular cavity was obtained utilizing an electronic digitizer (Graf/Pen Science Accessories Corporation) interfaced to a digital computer (Hewlett Packard) for calculating volumes The pattern of left ventricular contraction was determined by reviewing the superimposition of the end diastolic and end systolic silhouette and utilizing the terminology defined by Herman and associates.[25] Anterior and inferior wall abnormalities of contraction (asynergy) were considered separately Apical asynergy was grouped with anterior wall abnormalities, except when associated with inferior wall asynergy only In this latter case it was considered together with the inferior wall. Asynchrony and slight dyskinesia were not considered separately since they were always combined with asyneresis or akinesia The preoperative and postoperative studies for each group of patients were compared, utilizing the pair Student s t test In comparing the preoperative end diastolic volume or ejection fraction with that obtained postoperatively for an individual patient, a change of 15 per cent or more was defined as a significant change Fifteen per cent change in end diastolic volume and ejection fraction was arbitrarily chosen since there are no studies available comparing volume studies on the same patient from two separate cardiac catheterization procedures

Results

Left ventricular hemodynamics

Group I. The hemodynamic parameters evaluated pre and postoperatively in these patients are shown in Table II The left ventricular end diastolic pressure preoperatively exceeded 11 mm. Hg in 20 of the 47 patients comprising Group I Postoperatively in 15 of these patients the end diastolic pressure fell to normal. In three patients the end diastolic pressure was normal prior to surgery but abnormal postoperatively Comparing the results of individual patients before and after surgery, it was evident that in four patients of Group I the end diastolic volume decreased significantly (a change of 15 per cent

Table I Clinical background and bypass flow of patient series

	Group I Single grafts		Group II Double grafts	Group III Triple grafts
	1A LAD	1B RCA		
Number of patients	33	14	47	10
Age (yrs)				
Mean ± 1 S D	52 ± 10 4	56 ± 9 0	53 ± 8 3	52 ± 5 5
Range	33 74	32 66	34 72	45 62
Sex, M/F	28/5	11/3	44/3	10/0
Duration of angina (yrs)				
Mean ± 1 S D	1 5 ± 1 7	1 7 ± 1 4	2 4 ± 2 0	4 1 ± 3 6
Angina pectoris				
Class III or IV	16	8	30	6
Unstable angina	17	6	17	4
Myocardial infarc tion (by ECG)	3	5	14	3

patients (Group IA) with single grafts to the left anterior descending artery and 14 patients (Group IB) with grafts to the right coronary ar tery Group II consisted of 47 patients with a dou ble vein bypass procedure All but two of these patients had one of their grafts to the left an terior descending artery, while 33 patients had grafts to the right coronary artery and sixteen patients had grafts to the circumflex artery Group III consisted of ten patients with triple vein bypass grafts. The functional classification of these patients was based on the New York Heart Association criteria [19] Unstable angina pectoris was defined as multiple episodes of anginal pain occurring at rest lasting over ten minutes, only temporarily relieved by nitro glycerin, and associated with transient ST and/or T wave changes in the electrocardiogram (ECG) Patients diagnosed as having unstable angina were operated on the same day as the preoperative study A history of prior myocardial infarction was accepted only if documented by the referring doctor The ECG diagnosis of a myocardial infarction was based on accepted cri teria [20]

Methods

All studies were performed after drugs (i e anti arrhythmic drugs, digitalis, and pro pranolol) were discontinued for at least three days Preoperative studies consisted of right and trans septal combined with retrograde left heart catheterization The normal left ventricular end diastolic pressure for this laboratory is 11 mm. Hg or less. Left ventricular angiograms were ob tained by injecting 0 50 to 0 75 ml per kilogram of 90 per cent sodium meglumine diatrizoate into the left ventricle through the trans septal cathe ter while recording left ventricular pressure through the retrograde catheter Cineangio grams were taken with a 35 mm camera at 60 frames per second while recording the left ventricular pressure and ECG on the cine film (Cinetrace, Electronics for Medicine) and on pho tographic paper In many patients, after the com pletion of the injection of contrast material the trans septal catheter was promptly withdrawn so as to avoid ventricular premature beats When the left ventricular angiogram was completed, a grid of known dimensions was positioned at the approximate location of the left ventricle and filmed to permit correction due to magnification After completion of the left ventricular angio gram, selective coronary angiograms were performed in multiple projections using methods described by Sones and Shirey[21] or Judkins[22] Postoperative studies were performed in the same cardiac catheterization laboratory as the preoperative studies utilizing a percutaneous transfemoral approach for both the left ventricu lar and selective saphenous vein angiograms. The left ventricular angiograms were performed,

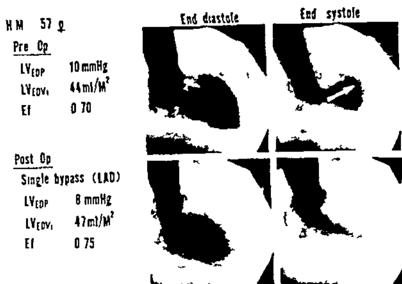


Fig 2 Preoperative and postoperative study in a 57 year-old housewife with Class III angina pectoris ECG revealed T wave inversion only in left precordial leads. Preoperatively the patient had isolated stenosis of the proximal left anterior descending artery with a normal right coronary and circumflex artery The antero-apical portion of the left ventricle demonstrates impaired movement (arrow) which, after surgery is no longer present Abbreviations LVedp = left ventricular end diastolic pressure LVedv = left ventricular end diastolic volume EF = ejection fraction

while 80 (77 per cent) patients had a normal contractile pattern after surgery (Fig 1) The changes noted postoperatively in the left ventricular angiograms were readily apparent (Figs 2 through 5) A normal preoperative contractile pattern with but one exception persisted postoperatively (Fig 1) This one exception was a patient who developed a coronary arteriovenous fistula as a complication of surgery and developed a localized area of apical akinesia of the left ventricle This latter patient was reported in detail[26] All patients but one with asyneresis of one wall of the left ventricle had normal contractile patterns after surgery One patient with inferior asyneresis and unstable angina pectoris had an intra operative myocardial infarction with postoperative inferior akinesia Only eight of 27 patients with akinesia involving one wall of the left ventricle had a normal contractile pattern after surgery (Fig 1) In the remaining 19 patients five patients had asyneresis and fourteen patients continued to demonstrate akinesia Postoperatively in nine patients with preoperative asynergy involving two walls of the left ventricle a normal contractile pattern was seen postoperatively in six patients improvement in two patients, and no change in one patient (Fig 1) Asyneresis was noted in 41 instances (27 one wall and seven two walls) prior to surgery Postoperatively 38 (93 per cent) patients had normal wall movement In contrast, of 29 instances of akinesia of a wall observed prior to surgery only eight (28 per cent) patients had a complete return of normal wall movement Return to a normal contractile pattern after surgery was accompanied by normal left ventricular end diastolic pressure in the majority of patients (71 per cent) whose end diastolic pressure was elevated prior to surgery However a return to a normal left ventricular end diastolic pressure after surgery was accompanied by a significant (greater than 15 per cent) reduction in the end diastolic volume in only eleven patients

The presence of unstable angina pectoris, when associated with an abnormal contractile pattern preoperatively did not appear to influence the reversibility to a normal contractile pattern when compared to the change noted in patients with class III or IV angina pectoris (Table IV) However the presence of abnormal Q waves on the ECG indicated that return to normal left ventricular contractile pattern was not likely although some improvement was possible (Fig 5 Table IV) As noted in Table IV of the 23

Table III Preoperative and postoperative hemodynamics in Group II (double bypass) and Group III (triple bypass) patients

No of patients	*Group II Double bypass 47*		*p*	*Group III Triple bypass 10*		*p*
	Preoperative	*Postoperative*		*Preoperative*	*Postoperative*	
Heart rate	80 ± 13	95 ± 14	<0 001	84 ± 13	100 ± 10	
Left ventricular						
End diastolic pressure (mm Hg)	13 ± 5 8	10 ± 4 7	<0 005	12 ± 7 6	9 ± 3 9	
End diastolic volume (ml /M²)	68 ± 16	64 ± 13		71 ± 15	61 ± 9	
Stroke volume (ml /M²)	41 ± 11	44 ± 9		43 ± 10	43 ± 7	
Ejection fraction	0 60 ± 0 13	0 69 ± 0 10	<0 001	0 61 ± 0 06	0 71 ± 0 07	<0 01
Stroke work (Gm m./bt /M²)	66 ± 20	67 ± 15		77 ± 25	69 ± 12	

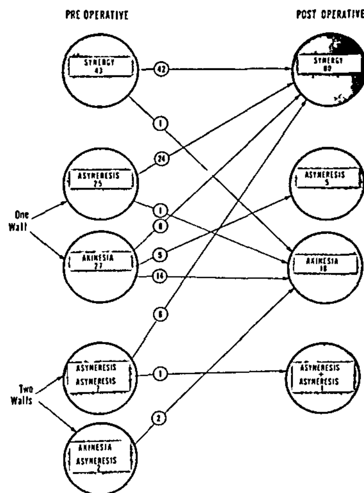


Fig 1 A summary of the preoperative and postoperative contractile pattern in 104 patients who underwent aortocoronary bypass surgery

or more) The ejection fraction increased significantly in three patients in Group I In no patient was there a significant increase in end diastolic volume or decrease in the ejection fraction

Group II The 47 patients with double vein bypass grafts (Table III) revealed a significant increase in heart rate and ejection fraction in postoperative studies as well as a decrease in end diastolic pressure Elevated end diastolic pressure noted prior to surgery in 25 patients fell to normal in 18 of these patients after surgery Three patients with normal end diastolic pressures prior to surgery showed increases to more than 11 mm Hg after surgery In no patient was there a significant increase in the end diastolic volume or a decrease in the ejection fraction

Group III As noted in Table III the only significant change in the left ventricular hemodynamics in the ten patients with triple vein grafts was an increase in the ejection fraction In no patient was there an abnormal increase in the end diastolic pressure postoperatively, while in four patients an elevated filling pressure observed preoperatively became normal after surgery

Left ventricular wall motion In the entire series of 104 patients, 43 (41 per cent) patients had a normal contractile pattern prior to surgery

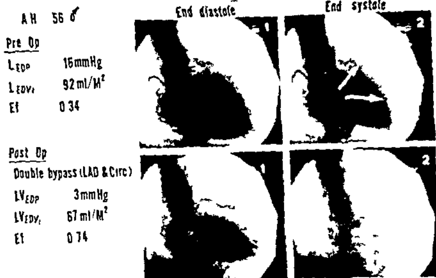


Fig 4 Preoperative and postoperative study of a 56 year-old man with unstable angina pectoris and proximal stenosis of the left anterior descending and circumflex artery and slight irregularity of the right coronary artery Note impaired left ventricular hemodynamics and marked impairment in contractile pattern of the left ventricle especially the entire anterior wall (arrow) At the time of study the ECG was normal and the patient had no angina pectoris After surgery (bypass to LAD and circumflex artery) the patient had a normal end diastolic pressure, a reduction of the end diastolic volume and a normal ejection fraction Note after surgery a normal contractile pattern For abbreviations see Fig 2

akinesia In the remaining eight patients improvement was noted in three patients and in five patients synergy remained after surgery despite the appearance of new Q waves In these ten patients the only hemodynamic parameter indicating an adverse change after surgery was an increase in the left ventricular end diastolic pressure noted in two patients (13 and 14 mm. Hg)

Discussion

The spectrum of left ventricular function resulting from coronary artery disease has been evaluated by others [27-29] The patients who form the basis of this report represent a select group since all the patients were referred only because of angina pectoris none of whom had complicating congestive heart failure or significant mitral insufficiency Congestive heart failure or significant mitral insufficiency when present in patients with arteriosclerotic heart disease are almost invariably accompanied by marked impairment in left ventricular function [27,29] Our management of such problems has included infarctectomy aneurysmectomy or mitral valve replacement combined with aortocoronary bypass surgery Improvement in contractility in these patients is probably due to the combination of mitral valve replacement or removal of non contracting myocardium together with increased coronary perfusion as a result of aortocoronary bypass Because this study was designed only to evaluate the role of aortocoronary bypass on left ventricular function patients requiring mitral valve surgery or infarctectomy and aneurysmectomy were excluded. In our experience the majority of patients referred because of intractable angina pectoris have normal end diastolic volumes An elevated end diastolic volume when present is usually accompanied by a decreased ejection fraction [27,29] At the present time because of the increased risk of surgery patients with an ejection fraction of 0 30 or less are not accepted for primary aortocoronary bypass surgery [30] However it should be emphasized that significant impairment in contractile pattern may still be present with a normal end diastolic volume and ejection fraction [27,29] which is readily discernible on the left ventricular angiogram (Figs 2 through 4) Because this study was designed to determine the optimal benefit derived from aortocoronary bypass surgery only patients were included who had all grafts patent that were placed at the time of surgery This is in contrast to other

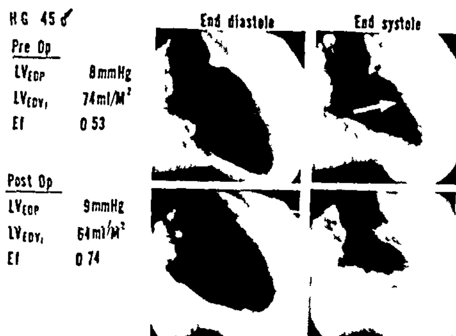


Fig 3 Preoperative and postoperative study in a 45 year old man with Class III angina pectoris ECG revealed T wave inversion only in the precordial leads Preoperatively selective coronary angiogram revealed proximal stenosis of the left anterior descending and circumflex artery The right coronary artery was normal Note the impaired wall movement of the anterior apical portion (arrow) of the left ventricle at end systole which after double bypass surgery (to LAD and circumflex artery) is no longer present For abbreviations, see Fig 2

Table IV Reversibility of abnormal left ventricular contractile pattern

	Number of patients with asynergy		*
	Preoperative	Postoperative	
Angina pectoris			
A – Class *III* or *IV*	32	17	N.S.
B – Unstable	29	6	
Electrocardiogram			
A – Infarction pattern (abnormal Q waves)	23	19	$p < 0.001$
B – No infarction pattern on electrocardiogram	38	4	
A – Unstable angina and infarction pattern on electrocardiogram	6	5	
B – Unstable angina and no infarction pattern on electrocardiogram	23	1	$p < 0.005$

Chi square test used to compare situations A and B

patients who had ECG evidence of a transmural myocardial infarction and asynergy preoperatively, 19 patients still had asynergy after surgery However, of 38 patients with no evidence of a transmural myocardial infarction and asynergy preoperatively, only four patients had asynergy after surgery ($p < 0.001$) In contrast, asynergy in the absence of abnormal Q waves on the ECG was likely to be associated with a return to a normal contractile pattern after surgery (Figs. 2 through 4) Asynergy present in 23 patients with unstable angina but without an infarction pattern on the ECG revealed that, after successful bypass surgery all but one patient had synergy (Table IV, Fig 3) However, six patients with unstable angina and ECG evidence of a transmural myocardial infarction revealed that after surgery, five patients still had asynergy

Ten patients developed a new Q wave on the ECG after surgery One patient with synergy and one patient with asyneresis went on to develop

However it should be noted that changes in wall motion after surgery were independent of changes in the heart rate Reversibility to a normal contractile pattern after surgery was not influenced by changes in heart rate when patients were grouped according to those who showed an increase after surgery and compared to those who showed no increase after surgery

Preoperative evaluation of clinical candidates for revascularization procedures is useful in predicting the degree and type of improvement of left ventricular function that may occur as a result of successful coronary bypass surgery As indicated in Table IV the type of anginal syndrome present and the ECG can predict prior to hemodynamic studies whether any localized disorders of contraction will be completely reversible Unstable angina pectoris by itself is not useful in predicting complete reversal to a normal contractile pattern after surgery However in the patient with unstable angina and no infarction pattern on the ECG complete reversal to normal left ventricular function can be anticipated in practically all subjects If hemodynamic and angiographic studies demonstrate impaired function preoperatively the ECG is useful in predicting reversal to normal function after surgery As indicated in Table IV only four patients out of 38 without infarction pattern on the ECG had an abnormal contractile pattern persisting after surgery whereas the majority of patients with abnormal Q waves in the preoperative ECG had varying degrees of asynergy persisting after surgery It should be emphasized, however that, although abnormal Q waves in the ECG indicate a return to normal contractile pattern is unlikely some improvement can still occur This is illustrated in Fig 5 in a patient with ECG findings of an old inferior wall myocardial infarction and single vessel disease of the right coronary artery The improvement in left ventricular contractile pattern after surgery is apparent although persistent lower inferior apical akinesia is present.

The type and location of the regional disorder in contraction found at the time of evaluation can be of value in predicting the degree of reversibility expected with successful aortocoronary bypass surgery All but one patient with asyneresis involving one wall had a return to a normal left ventricular contractile pattern (Fig 1) The one exception was a patient with unstable angina pectoris who had an intra operative myocardial infarction This is in sharp contrast to the 28 patients who had akinesia of one wall of whom only eight patients (28 per cent) had a return to normal contraction while the majority of such patients demonstrated no change Asynergy involving two walls of the left ventricle reveals that after surgery asyneresis is more likely to demonstrate complete reversal as compared to akinesia (Fig 1) Similar findings were noted by Saltiel and co workers[14] in 15 patients with akinesia and eight patients with asyneresia. Furthermore anterior wall abnormalities are more likely to be completely reversible when compared to inferior wall abnormalities The difference in behavior of the inferior wall as compared to the anterior wall is probably related to the ECG patterns present. Of 25 patients with infarction pattern on the ECG before surgery 18 patients had involvement of the inferior wall while only eight patients had abnormal Q waves in the anterior leads Thus the failure to demonstrate complete reversibility of the inferior wall contractile pattern is most likely related to the predominance of pre existing inferior lead Q waves reflecting varying degrees of myocardial fibrosis

From these observations on the changes in left ventricular wall movement accompanying successful aortocoronary bypass surgery it must be concluded that regional disorders in contraction in ischemic heart disease especially when not accompanied by abnormal Q waves on the ECG reflect functional disturbances in the contractile process as a result of ischemia and as such are reversible once the ischemia is relieved It should be emphasized that our observations and conclusions are based on a short term study on a select group of patients Similar long term studies are not available but are needed to determine whether such observations noted by us as well as others, can be anticipated after such surgery The stage of irreversibility in any particular patient is hard to predict. However our experience as well as that of others [13, 15, 16] strongly suggests that the patient with unstable angina pectoris may be approaching a stage where irreversibility may be anticipated if surgery is not performed. We have seen many examples of ominous preoperative left ventricular angiograms (Fig 3) in patients with unstable angina suggesting imminent irreversible changes. However even in the patient with stable Class III or IV angina pectoris such changes may be seen (Fig 4) Myocar

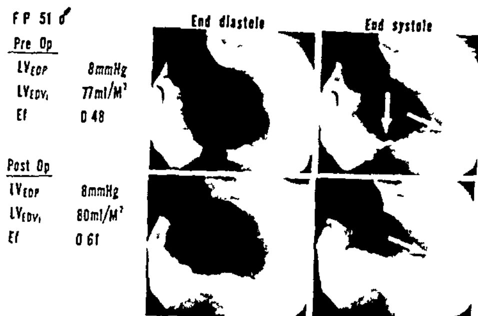


Fig 5 Preoperative and postoperative study of a 51 year-old man with Class IV angina pectoris The ECG revealed prior to surgery abnormal Q waves in Leads II III and aV_F diagnostic of an old inferior myocardial infarction Selective coronary angiogram demonstrated single vessel disease of the right coronary artery with over 95 per cent proximal stenosis and good runoff Preoperative angiogram demonstrated impaired wall movement of the inferior and apical wall (arrow) at end systole Note that after the right coronary bypass surgery there is still persistence of apical wall movement impairment (arrow) and that after surgery the ejection fraction is normal For abbreviations, see Fig 2

studies which have included a smaller number of patients, some of whom have had graft closure [12 14 16 18] Finally, patients were selected for this study only if the preoperative and postoperative angiographic studies were technically good enough for evaluating the contractile pattern of the left ventricle

Our experience as well as observations made by others [12 16] indicate that, in the majority of patients having abnormal left ventricular function and angina pectoris, successful aortocoronary bypass surgery will result in improved myocardial function The early observations in dog experiments by Tennant and Wiggers[31] indicated that during acute myocardial ischemia an abnormality of left ventricular contraction pattern develops, which is reversible once the ischemia is relieved These observations were corroborated in man by Chatterjee and co workers,[13] who demonstrated in six patients with unstable angina pectoris and marked depression of left ventricular function, dramatic reversal to normal myocardial function after aortocoronary bypass surgery Further observations by these same authors[15] in ten patients indicated that even in chronic ischemia reversal to a normal or improved left ventricular function may accompany successful bypass coronary surgery The present observations in our 104 patients unquestionably confirm these observations Such improvement, noted early after surgery, is usually sustained one year later if the bypass grafts remain patent [16]

Patients with angina pectoris have been noted to have transient left ventricular failure[32] and temporary changes in ventricular wall movement as a result of atrial pacing[33] or propranolol administration[25] as well as improvement in myocardial contractile pattern after epinephrine administration [25] These observations indicate that the abnormal left ventricular hemodynamics and regional disorders of wall movement of ischemic heart disease may represent functional disturbances which are partially or completely reversible The surgical experience of others [12 16] as well as our own, appear to confirm this concept In all patients studied in the present series drugs were discontinued at least three days prior to hemodynamic study No patient had angina pectoris during the hemodynamic study, although angina was not uncommon during selective coronary arteriography It is interesting that the postoperative studies in many patients were accompanied by a significant increase in heart rate when compared to the preoperative study Similar observations have been noted by others [13 16] Such changes in heart rate may affect hemodynamic studies

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dial fibrosis as a result of a myocardial infarction represents a stage of irreversibility The role of asynergy in the pathogenesis of congestive heart failure with arteriosclerotic heart disease has already been emphasized.[25] Coronary artery bypass surgery for congestive heart failure complicating arteriosclerotic heart disease carries a high mortality and the results are generally poor [34] Patients with arteriosclerotic heart disease and congestive heart failure almost invariably demonstrate multiple abnormal Q waves on the ECG indicating one or more previous myocardial infarctions According to our observations, such abnormal Q waves would indicate irreversible myocardial damage and poor results from a bypass procedure could be anticipated Removal of such irreversible non contractile segments has generally been accompanied by improvement in cardiac performance [35,36]

In ten of our patients, abnormal Q waves were noted after surgery Previous reports indicate that new Q waves after coronary bypass surgery occur in nine[1] to as high as 20 per cent[39] of the cases. In only two of our patients was there deterioration of left ventricular wall movement, while in the remaining eight patients, left ventricular contractile pattern either remained normal or became normal This was an unexpected finding and would suggest that the infarction was too small to manifest itself in any functional disturbances or that the changes in the ECG are due to a localized conduction disturbance It is interesting that new Q waves in eight patients, without hemodynamic or angiographic deterioration became evident in the recovery room and in five patients were not followed by serial changes In the last 100 surgical patients, the frequency of abnormal Q waves occurring after surgery has dropped to seven per cent The only change in surgical technique in these latter patients has been the use of a transatrial rather than an apical ventricular vent during cardiopulmonary bypass This suggests that the higher frequency of new Q waves developing after surgery in our early cases may have been due to surgical venting techniques, resulting in either a conduction disturbance or direct local damage of the myocardium

Summary

Left ventricular hemodynamics and contractile patterns were evaluated in 104 patients before and after aortocoronary bypass surgery Patients were selected on the basis of referral for surgery because of angina pectoris and the demonstration, postoperatively, of all grafts being patent. Group I consisted of 47 patients with single grafts (LAD 33 and RCA 14) Mean left ventricular end diastolic pressure, volume, and ejection fraction revealed no change after surgery Twenty four patients had asynergy prior to surgery, of these 24, 16 patients had a normal contractile pattern after surgery Group II consisted of 47 patients with double vein grafts. Postoperatively, there was a significant decrease in left ventricular end diastolic pressure ($p < 0.005$) and increase in ejection fraction ($p < 0.001$) Asynergy in 29 patients preoperatively revealed synergy after surgery in 15 patients Group III consisted of ten patients with triple vein grafts Ejection fraction increased postoperatively ($p < 0.01$) All but two of the eight patients with asynergy preoperatively showed synergy after surgery In the entire group of patients 43 with synergy preoperatively, with but one exception had synergy after surgery Asynergesis in 41 instances preoperatively revealed postoperatively that 38 patients (93 per cent) had normal wall movement. In 29 instances of preoperative akinesia of one wall only 8 patients (28 per cent) showed a return to normal wall movement Unstable angina pectoris alone did not influence reversibility of abnormal contractile patterns Unstable angina pectoris with absence of abnormal Q waves in the ECG was noted in 23 patients with asynergy all but one of these patients had a normal contractile pattern after surgery Patients with infarction pattern on the ECG when accompanied by asynergy, were unlikely to have a normal contractile pattern after surgery (4 out of 23 patients) Reversibility of left ventricular function after surgery is common not related to number of grafts, but is related to type of wall abnormality noted prior to surgery as well as the ECG and clinical state of the patient.

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Effects of human contact on the heart activity of curarized patients in a shock-trauma unit

James J Lynch, Ph D
Lois Flaherty, M D
Carol Emrich, R N , M S
Mary E Mills, R N , M S
Baltimore Md
Aaron Katcher, M D
Philadelphia, Pa.

Physicians use the terms "art of medicine' or "bedside manner' to describe that important aspect of medical practice which includes behaviors having profound emotional and physiologic effects on patients Using a descriptive phrase such as art of medicine implies that the quality of the physician's actions producing these effects is different from the techniques used in "scientific" medicine That is, it is generally believed the 'art of medicine involves phenomena that seem to elude precise scientific designation and are so inconstant that precise designation or dissection into a set of measurable variables is difficult, if not impossible to accomplish

Perhaps the most universally recognized aspect of bedside manner is the ability of the physician and other medical personnel to influence the measurement of blood pressure heart rate and other variables of cardiovascular performance Indeed, this ability was recognized almost simultaneously with the discovery of the human pulse For example about 30 A D Aurelius Cornelius Celsus described the art of pulse taking in "*De Medicina*' as follows[1]

> 'On the contrary bathing, exercise fear and anger, and any other state of mind may often be apt to excite the pulse, so that when the medical man first comes the anxiety of the patient, who is in doubt as to what he may seem to him to have may upset the pulse For this reason it is not the part of an experienced doctor that he seize the arm with his hand at once, but first of all sit down with a cheerful expression and enquire how he feels and if there is any fear of him to calm the patient with agreeable talk, and then at last, lay his hand on the patient's body How easily a thousand things may disturb the pulse which even the sight of a doctor may upset!"

And yet in spite of both the antiquity and the ubiquity of this knowledge the magnitude generality, and most importantly the mechanisms of the effects of human contact on the cardiovascular system have not received careful attention This lack of attention is due, in part, to the complex nature of clinical interactions which are difficult to reduce to simple experimental models and in part to the commonness of the knowledge that the phenomenon exists

Recently, we have described the effects of human contact on cardiac responses of patients in coronary care units (CCU) In these patients even the simple act of taking the pulse produces significant changes in heart rate and more importantly can double the frequency of ectopic beats [2-5] The cardiac effects of human contact have also been demonstrated in a series of experimental models developed to clarify some of

From the Department of Psychiatry University of Maryland Medical School and the School of Nursing University of Maryland Hospital Baltimore and the Department of Psychiatry School of Medicine Division of Behavioral Sciences School of Dental Medicine University of Pennsylvania Philadelphia

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Reprint requests to Dr James J Lynch Department of Psychiatry University of Maryland Medical School Baltimore Md 21201

the environmental physiologic and genetic mechanisms involved in these reactions For example in both dogs and horses various routine types of human contact have been shown to produce large and at times profound cardiovascular changes[6,11] These changes persist when the animal is paralyzed with curare indicating the central origin of the responses.

Our observations on the effects of human contact on the cardiac activity of CCU patients raise important questions about possible mechanisms that may meditate these heart reactions For example were the cardiac changes observed in CCU patients the result of respiratory or muscular changes? Are changes in the frequency of ectopic beats during routine medical interactions such as pulse taking idiosyncratic to patients with cardiac pathology? The current practice of using d tubocurarine in a variety of clinical emergencies in a hospital shock trauma unit provided a unique opportunity to answer some of these questions By observing patients with and without cardiac pathology in whom respiration and muscular activity were controlled and whose heart rate and blood pressure were constantly monitored, the mechanisms and magnitude of cardiac reactions to human contact could be assessed

Method

The patients in this report were the first four curarized patients analyzed by us from a larger series of 40 critically injured patients monitored in our University Hospital Shock Trauma Unit These patients all had varying types of respiratory support when monitored by us In the larger series of patients to be discussed elsewhere 20 patients were artifically respirated tracheostomy patients, 10 of whom were maintained on d tubocurarine 10 patients were receiving humidified O_2 via a tracheostomy tube and 10 patients had no artificial respirating support. All curarized patients were monitored by us regardless of their mental state or physical condition

Physical description of unit The patients in this study were those that had been admitted to the Maryland Center for Emergency Services of the University of Maryland Hospital This Center was established for the aggressive treatment of severe medical emergencies that usually involved shock and trauma This center is a twelve bed air conditioned rectangular unit approximately 50 feet by 40 feet A 9 by 12 foot octagonal central monitoring station was in the center of the unit elevated 1½ feet above the unit floor for unobstructed vision This central station had desks for clinical personnel telephones patient records central monitoring equipment and a computer operated scanning unit that monitored all patients Twelve beds surrounded this station three against each wall All but two beds were open to the center of the unit and were separated from each other by a floor to ceiling partition of which the lower four feet was metal and the upper was glass The beds could be screened by manual partitions although no curtains or other obstructive devices were built in Each 11 by 7 foot bed unit was completely autonomous having medical and patient care supplies refrigerator sink and running water Engstrom respirator wall suction wall air and oxygen equipment for continuous routine recording of the electrocardiogram systolic and diastolic blood pressure and venous pressure as well as capability for the optional recording of cranial pressure temperature and pulmonary pressures. At the central station all patients electrocardiograms (ECG) arterial and venous pressure waves could be printed out on paper on command or a digital monitoring system could display all moment to moment physiologic fluctuations as they occurred. A computer analyzed and displayed blood gas readings while surveying each of the twelve beds every hour subsequently printing out time heart rate blood pressure temperature respiration and other events being monitored.

Procedure The purpose of this study was to replicate aspects of the observations previously made in our University CCU[2,5] with patients in the Shock Trauma Unit who were on d tubocurarine and artificially respirated. Two types of interactions were studied. the first type was relatively simple spontaneous clinical interactions such as a doctor s visit in which neither the patient nor staff were aware they were being observed. The second type was planned interactions in which one of two graduate nurses who were aware of the purpose of the study either took the patient s pulse or held the patient s hand or touched their arm and verbally comforted them with the following types of statement

(First name of patient) my name is (first

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Results

Patient No 1 The first patient was a 31 year old white female who suffered multiple injuries as a result of an auto accident. She had lacerations of the liver; bilateral pneumothoraces and fractures of the face ribs femur and ankles. On admission she was described as combative and delirious but became alert and followed commands by the second hospital day Her hospital course was complicated by persistent abdominal bleeding, persistent pneumothorax despite chest tubes, pneumonia and finally septicemia and massive upper gastrointestinal tract bleeding *She remained on a respirator* with tracheostomy She was curarized on the sixteenth hospital day because of acute respiratory problems and remained curarized for the following eight days At the time of curarization she was described as alert and remained so until the day before her death 38 days after admission to the hospital *The patient was observed* on the twenty third day after admission At this time she was on 12 mg d tubocurarine intravenously every hour

We monitored three episodes of human contact in this patient two of which the nurse held the patient s hand and comforted the patient, while in the third interaction a nurse simply took the patient s pulse for one minute Fig 1 shows this patient s reaction during the first interaction in which a nurse held this patient s hand and comforted her Several reactions outlined in this *figure deserve* notice First of all the heart slowed abruptly to a rate of 72 beats per minute when the nurse first held the patient s hand. The average heart rate before the nurse approached the patient s bedside was 84 beats per minute the lowest rate was 80 beats per minute and the highest rate was 108 beats per minute While the nurse comforted the patient *six prolonged R R* intervals occurred, each of which were twice as long as the average *beat to beat heart rate* Approximately 20 seconds after the nurse left the patient s bedside a premature ventricular contraction (PVC) occurred This was the only PVC that occurred during the entire time the patient was monitored by us, a total of 26 minutes and 45 seconds The nurse s departure from the patient s bedside was followed by a heart rate increase

The second time the nurse held the patient s hand and comforted her the *heart rate fell* abruptly from an average rate of 104 beats per minute during the two minute period pre entry down to 92 beats per minute with two prolonged R R intervals However after the nurse left the bedside the heart rate did not accelerate noticeably but maintained an average *rate of* 98 beats per minute during the three minute post period.

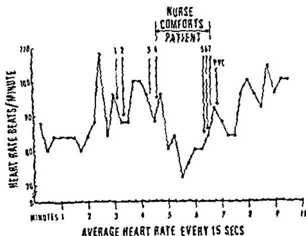


Fig 1 Fifteen second heart rate averages of *patients before* during and after nurse comforting patient Averages are computed by multiplying the number of R waves in a 15 second period by four Note decrease in heart rate during comforting and PVC following nurse s departure Key (1) nurse No 1 putting away supplies (2) nurse No 1 leaves unit (3) nurse No 2 enters unit (4) nurse No 2 holds patient s hand and talks to her (5) nurse No 1 enters and looks at monitor (6) nurse No 1 leaves unit and (7) nurse No 2 stops and leaves unit.

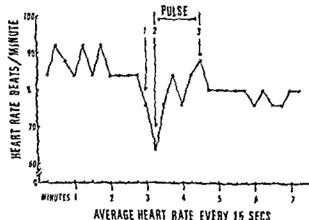


Fig 2 Patient s heart rate averaged every 15 seconds before during and after pulse taking by nurse Note decrease in heart rate during pulse taking Key (1) nurse enters (2) nurse takes pulse and (3) nurse stops and leaves

Fig 2 shows the patient s heart rate reaction when the nurse simply took the patient s pulse for one minute As can be seen in Fig 2 the heart

name of nurse) and I am a nurse I know you can t answer me when I talk to you even though you can hear me That's because of your medication You re receiving a drug called curare which has temporarily para lyzed you so that you are unable to respond in any way The drug has also blocked your respiration so there is a machine at your bedside breathing for you which you may be able to hear This medicine is an unpleasant but very necessary part of your therapy so please try to relax and bear with it As I said before the effect will only be temporary and once the drug is discontinued you will be able to move as before We will try to antici pate your needs since you are presently un able to communicate them to us There is al ways a doctor or nurse at your bedside so please try not to worry

This statement was not memorized or delivered verbatim, but rather the nurse reacted to each patient in an individualized manner Whenever possible a three minute resting period prior to and following both types of interaction was obtained. While in one sense holding a pa tient s hand was among the simplest clinical in teractions that we could analyze even this in teraction proved to be quite difficult to study within the context of the Shock Trauma environ ment Various clinical personnel were almost al ways at the patient s bedside and it was not un common for as many as 7 to 8 physicians and 4 to 5 nurses to be around the patient's bedside Coupled with this intense clinical attention the telephones at the central stations were con stantly ringing and the paging intercom system was frequently calling various individuals The various patient monitoring devices also had audi tory cues Given this complex array of stimuli we frequently had to watch a curarized patient for as long as 2 to 3 hours before a period would oc cur in which the patient was left unattended for as long as seven minutes the minimum time period necessary to evaluate patient reactions Since the patients were curarized for various periods of time we had no precise means of determining whether the patient was conscious during the interactions We relied on the attend ing physician's general assessment of mental status during periods when the curare effect was transiently reversed However, one of the pa tients to be discussed in this report (patient 4) was studied immediately after he was given d tubocurarine Since he was talking with the phy sician as he was being given d tubocurarine it is reasonable to assume that he was conscious dur ing our observations The research team did not participate in any clinical decision regarding these patients and had no prior knowledge as to when a patient might be curarized We were able to monitor these patients only by remaining on 24 hour call

Data analyses. Data were collected on poly graph paper run at a speed of 25 mm per sec ond One channel paper was used if the ECG alone was monitored, and when arterial pressure was available four channel paper was used. These recordings were obtained from the central console The patients and staff were not aware of which patient and/or what we were observing This method did, however, present one problem If a patient in another bed should suddenly drop below or above safety range in any of the param eters being monitored the central monitor would automatically switch over to that bed to record the change In analyzing the data these inter ruptions are indicated by a dotted line In this paper, only ECG changes will be reported Rate changes were detected by two methods (1) measuring R to R intervals with a Lansing ECG rule calibrated to 0 05 cm then converting this number into heart rate and (2) counting the R waves in each successive 15 second period and multiplying by four thereby obtaining four measures of heart rate each minute All records were analyzed at least twice and if any discrep ancies in the analyses were noted they were counted a third time

The observations were conducted by two grad uate nurses, who alternately (1) collected data marking the beginning and end of each social in teraction in pencil on the polygraph paper and (2) interacted with the patients Both nurses were aware of the purpose of the study Graduate nurses were used both because of their famil iarity with the milieu of the shock trauma unit and because they were routinely assigned obser vation duties in this unit Therefore no special attention would be paid to their presence in this unit One of the nurses (MEM) had participated in prior CCU studies and was quite familiar with the research protocol used in these studies

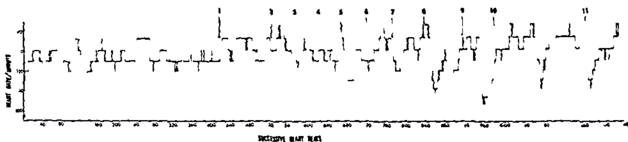


Fig 4 Beat to beat heart rate of patient while nurse cleans and retapes I V insertion site See text for discussion Key (1) turning arm with I V and retaping it, (2) changing tape (3) stopped (4) touched patient and stopped (5) touched patient and stopped (6) applying Betadine (7) working with I V disconnecting it (8) rechecking tubing (9) applying bandaid (10) applying tape and (11) stopped.

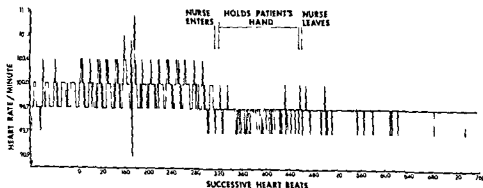


Fig 5 Beat to-beat heart rate of patient before during and after nurse holds patient s hand and comforts him Note decrease in heart rate during and after nurse s contact with patient

bandaid was being changed The pattern and magnitude of both heart rate acceleration and subsequent deceleration were similar to that observed when the nurse simply held this patient s hand as was shown in Fig 3

These two events were the only interactions we were able to monitor in this patient

Patient No 3 The third patient was a 54 year old white male with a history of coronary artery disease and mitral insufficiency who underwent saphenous vein bypass and mitral valve replacement He had a past history of anxiety attacks and alcoholism An initial electrocardiogram showed ST depression but no other abnormalities At the time of surgery the right coronary artery was found to be completely obstructed and the right papillary muscle had been ruptured The immediate postoperative period was complicated by hemolysis atrial arrhythmia and hypotension and the patient was transferred to the Shock Trauma Unit for management of these problems He continued to require isuprel and aramine to maintain his blood pressure and had various cardiac conduction disturbances ranging from nodal tachycardia to A V dissociation with a junctional rhythm At the time of the study rhythm was junctional with retrograde conduction On the fifth postoperative day he developed ventricular fibrillation and died

Although the patient was described as alert and responsive on the first postoperative day his mental status deteriorated afterward He was placed on d tubocurarine in order to prevent his respiration from becoming out of phase with the respirator During periodic reversals of the curare effects he was described as ranging from *semiconscious* to unconscious and comatose Our observations were made from 1 to 2 hours before the patient s death at which point the patient was described as comatose

In all we monitored three interactions in this patient that occupied a total of 23 95 minutes During the first two interactions no significant heart rate changes were observed. These two interactions involved a nurse taking the patient s pulse and a nurse measuring central venous pressure In neither of these interactions did the

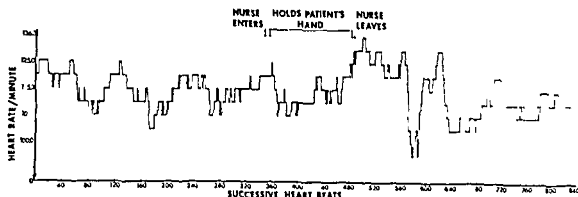


Fig 3 Beat to beat heart rate of patient before during and after nurse holding patient s hand. R R intervals are converted to rate per minute Note increase and then abrupt decrease in heart rate at cessation of hand holding

rate abruptly slowed as the nurse approached the bedside and took the patient's pulse The average heart rate for the three minute period pre entry was 86 beats per minute and slowed as low as 64 beats per minute during pulse taking After the nurse left the bedside, the average heart rate was 79 beats per minute

Patient No 2 The second patient was an 11 year old white female who was hospitalized after having been struck by a car She sustained a left frontal skull fracture and cerebral contusions as well as multiple pelvic fractures and a retroperitoneal hematoma Initially comatose by the eighth hospital day she was described as alert and oriented with no localizing neurologic signs when she rather suddenly became restless and confused and began to have marked respiratory distress which was later attributed to tracheal stenosis and mucous plugs Subsequently, tracheostomy and bronchoscopy were performed and adequate ventilation was obtained with a volume respirator She was curarized during these procedures because of her extreme restlessness and confusion and at the time of the study had been on curare two days Periodic reversals of curare over the next several days revealed her mental state to be that of delirium The patient subsequently recovered fully and was discharged after 33 days in the hospital On the day of our observations the patient was receiving d tubocurarine at a maintenance dose of 9 mg per hour intravenously She was on an Engstrom respirator set at 20 cycles per minute without any sighs

Two relatively uncomplicated clinical interactions were monitored in this patient Fig 3 shows the heart rate changes that occurred during a continuous 7 25 minute period when a nurse came to the bedside and held the patient s hand The nurse did not speak to the patient during this interaction As can be seen in Fig 3, for the three minutes before the nurse approached her bedside, the patient s heart rate was cycling rather rhythmically from a maximum beat to beat rate of 125 beats per minute to a low of 105 beats per minute No unusual changes in heart rate were observed during most of the period that the nurse held her hand However just as the nurse let the patient s hand go the heart rate increased to a peak rate of 136 beats per minute and then fell to about 95 beats per minute before cycling back into the the pre entry pattern During this entire 7 25 minute observation period, both the highest and lowest beat to beat heart rates occurred within 30 seconds after the nurse let the patient s hand down

Fig 4 shows similar heart rate changes that occurred during one of the clinical interactions that patients routinely experience in the Shock Trauma Unit In this interaction which occupied a total of 9 55 minutes a nurse came to the patient s bedside to adjust an intravenous (IV) drip and change the bandaid holding the IV needle in the patient's arm

Before the series of events outlined in Fig 4, the nurse had been writing at the bedside of the patient However until event No 1 she did not touch the patient As can be seen in Fig 4 a series of repeated episodes of physical contact with the patient occurred while the nurse changed the bandaid that was holding the IV needle in the patient s arm While this procedure may or may not have been associated with some degree of minor physical discomfort it is unlikely that any major discomfort was produced Nevertheless as can be seen in Fig 4, the heart rate pattern of this patient was altered while the

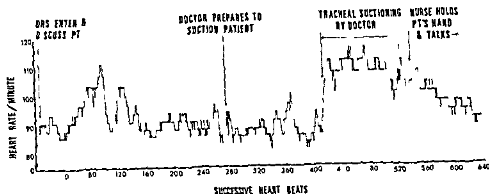


Fig 7 Beat to-beat heart rate of patient during Doctors rounds tracheal suctioning and comforting by nurse See text for discussion.

during a one minute period. It is of interest to note that the maximum heart rate increase while seven doctors were discussing the patient was almost as great, although not as sustained, as that heart rate change elicited during tracheal suctioning Immediately after tracheal suctioning a nurse spontaneously held the patient s hand and comforted him and the patient s heart rate began to immediately and steadily slow back to the pre suctioning level

However precisely after the six hundred fortieth heart beat shown in Fig 7 the patient s wife telephoned the unit and for the following 5 5 minutes a nurse held the telephone to the patient s ear and the patient s wife spoke to him Averaging the heart rate each 15 seconds during this period revealed that during the first minute of this conversation the patient s heart rate immediately increased once again to 100 beats per minute Again it should be noted that this rate increase was almost as great as the change during tracheal suction After the first minute however the patient s heart rate progressively slowed down until he was averaging between 80 and 84 beats per minute quite regularly for the last two minutes of this conversation

On both day two and day three the patient s resting heart rate was approximately 82 beats per minute

Discussion

In this study we have attempted to gather descriptive clinical data in humans that would parallel observations previously made in other clinical situations as well as replicate more precisely controlled animal studies[2-11] It should be emphasized that no attempt was made in this study to present a precisely timed series of repeated experiments The acute nature of the clinical situation precluded such formal experimentation Indeed, some of the events monitored in this study would be impossible to ever replicate within the precise context that they occurred They were simply unique human interactions For example we have never since observed a curarized patient listening to a telephone call from his wife precisely when we happened to be recording the patient s heart rate Nor have we since held the hand and comforted another comatose patient one hour before his death We recognize that the heart rate changes seen in this patient at the very point the nurse held his hand could have been due to chance and indeed there is no way to repeat the observation to conclusively answer the question In every sense these were unique and poignant human interactions and the uniqueness of these observations from an empirical point of view must be recognized as both a strength and an unavoidable weakness

In spite of the complexities inherent in these observations however we feel the data permit the strong inference that the heart rate of these patients was altered by these human interactions It is tempting in this situation to infer an emotional effect of the observed interactions but it is not possible to do so because we have no data other than the heart rate changes

In the four patients studied heart rate changes were observed in association with various types of human contact These observations indicate that heart rate changes observed during human contact (1) are not idiosyncratic to patients with intrinsic cardiac pathology who had been studied previously[2,5] (2) occur in patients whose musculoskeletal movements are

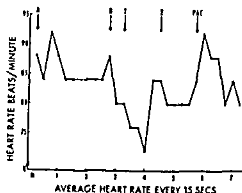


Fig 6 Beat to beat heart rate of patient before during and after pulse taking by nurse Note PAC following pulse taking Key (A) person in but remaining quietly by bedside and (B) person out (1) Nurse takes pulse and (2) nurse stops taking pulse and leaves

nurse speak to the patient The final interaction monitored in this patient occurred about an hour before death In this interaction the nurse came in held the patient s hand and quietly comforted the patient As can be seen in Fig 5 the patient's heart rate and its variability changed abruptly during and after this interaction from a resting average of 100 to an average of 96 during and after contact During this entire period the pa tient was in a junctional rhythm and no elec trocardiographic changes (other than the rate change) were noted during or immediately after the interaction

Patient No 4 The fourth patient was a 30 year old white male who suffered anoxic brain damage as a result of traumatic asphyxia caused by a crush injury to the chest. In addition he had a left brachial plexus injury On admission to the Shock Trauma Unit he was described as coma tose but within a few hours he progressed to delirium Following endotrachial intubation a tracheostomy was performed and adequate pulmonary ventilation was obtained with curare being used to control motor activity The patient was observed by us on both the second and third hospital days On both days he was described as having a clouded sensorium but responded ap propriately to pain and simple commands On the second hospital day, the patient was not given d tubocurarine, while on the third day he was curarized and artificially respirated

On his second hospital day, the patient was being administered oxygen via a *tracheostomy without curare* We monitored three separate in teractions on this day the first involved a nurse taking the pulse, the second involved a physi cian's examination, and the third involved a nurse holding the patient's hand and comforting him Fig 6 shows the abrupt heart rate decelera tion that occurred when the nurse took the pa tient's pulse Within 90 seconds after the nurse finished taking the pulse a premature atrial con traction occurred As with patient No 1 this was the only ectopic beat we observed during the en tire period we monitored this patient The second interaction involved a nine minute neurologic ex amination Before this examination the pa tient's resting heart rate was 80 to 84 beats per minute and rose to a maximum of 92 beats per minute when the physician instructed the pa tient to try to move his legs and toes After the examination was finished the patient s rate re turned to 80 to 84 beats per minute During the third interaction in which the nurse held the pa tient's hand and comforted him the resting heart rate before the interaction was 84 beats per minute and that rate did not change during the interaction However, within 30 seconds after the nurse put the patient's hand down the heart rate rose 92 beats per minute (averaged each 15 seconds), fell to 76 beats per minute and then peaked again at 92 beats per minute before re turning to the pre entry pattern It should also be noted that the heart rate of 92 beats per minute was the maximum rate that occurred when the doctor instructed the patient to try and move his leg Finally, it should be pointed out that this pat tern of heart rate acceleration, followed by heart rate deceleration was very similar to the pattern of heart rate reactions shown by patients Nos 1 and 2 during a similar type of interaction under curare

On the third hospital day the patient was given d tubocurarine and artificially respirated on an Engstrom respirator set at 20 cycles per minute without any sighs At the time of our ob servations, he was given d tubocurarine at a maintenance dose of 12 mg per hour, in travenously Just before he was given the d tubocurarine he was talking to the physician at the bedside Only one complex interaction parts of which are outlined in Fig 7, was monitored by us Our monitoring began right after the patient was first curarized and seven doctors came to his bedside As is shown in Fig 7, shortly after the doctors came to the patient s bedside tracheal suctioning was initiated at which time the pa tient was taken off the respirator several times

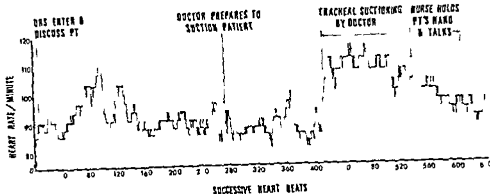


Fig 7 Beat to-beat heart rate of patient during Doctors rounds tracheal suctioning and comforting by nurse See text for discussion.

during a one minute period. It is of interest to note that the maximum heart rate increase while seven doctors were discussing the patient was almost as great, although not as sustained, as that heart rate change elicited during tracheal suctioning Immediately after tracheal suctioning a nurse spontaneously held the patient s hand and comforted him and the patient s heart rate began to immediately and steadily slow back to the pre suctioning level.

However precisely after the six hundred fortieth heart beat shown in Fig 7 the patient s wife telephoned the unit and for the following 5 5 minutes a nurse held the telephone to the patient s ear and the patient s wife spoke to him Averaging the heart rate each 15 seconds during this period revealed that during the first minute of this conversation the patient s heart rate immediately increased once again to 100 beats per minute Again it should be noted that this rate increase was almost as great as the change during tracheal suction After the first minute however the patient s heart rate progressively slowed down until he was averaging between 80 and 84 beats per minute quite regularly for the last two minutes of this conversation

On both day two and day three the patient s resting heart rate was approximately 82 beats per minute

Discussion

In this study we have attempted to gather descriptive clinical data in humans that would parallel observations previously made in other clinical situations as well as replicate more precisely controlled animal studies [2 11] It should be emphasized that no attempt was made in this study to present a precisely timed series of repeated experiments The acute nature of the clinical situation precluded such formal experimentation Indeed some of the events monitored in this study would be impossible to ever replicate within the precise context that they occurred They were simply unique human interactions. For example we have never since observed a curarized patient listening to a telephone call from his wife precisely when we happened to be recording the patient s heart rate Nor have we since held the hand and comforted another comatose patient one hour before his death We recognize that the heart rate changes seen in this patient at the very point the nurse held his hand could have been due to chance and indeed there is no way to repeat the observation to conclusively answer the question In every sense these were unique and poignant human interactions and the uniqueness of these observations from an empirical point of view must be recognized as both a strength and an unavoidable weakness

In spite of the complexities inherent in these observations, however we feel the data permit the strong inference that the heart rate of these patients was altered by these human interactions It is tempting in this situation to infer an emotional effect of the observed interactions but it is not possible to do so because we have no data other than the heart rate changes

In the four patients studied heart rate changes were observed in association with various types of human contact These observations indicate that heart rate changes observed during human contact (1) are not idiosyncratic to patients with intrinsic cardiac pathology who had been studied previously [2 5] (2) occur in patients whose musculoskeletal movements are

blocked and who are respired regularly, (3) occur in the context of what would seem to be intense sensory bombardment, and (4) can be of a magnitude equivalent to such strong physical stimuli as tracheal suction which also involves the momentary turning off of the curarized patient's *respirator*

Although curarization allows the heart rate changes to be observed independently of motor activity, it undoubtedly alters the patient's response to the environmental stimuli and, therefore, probably alters cardiac reactivity to such stimuli The meaning of human contact to a totally paralyzed, completely passive and helpless person can in no way be considered in the light of everyday normal experiences In addition these patients were all seriously ill (two died) most likely in some degree of physical discomfort, and with at least some clouding of con*sciousness* Under curare they were unable to move or talk

Only two of the four patients in this study were described as probably being conscious the mental state of the others ranged from delerious to *comatose during periods* when the curare was reversed It is important to note, however that it was impossible to assess the patient s level of consciousness *precisely* at the time of the study The *relationship between* heart rate responsivity and *level of consciousness remains* unclear[12]

In evaluating the significance of these data two widely held, contradictory, but frequently simultaneously held attitudes must be recognized One attitude is that the data are trivial in the *sense of being self* evident The second attitude is that the situation that generates these heart reactions is too complex to evaluate Common sense or common knowledge tells us that noxious environmental stimuli or stimuli that change *emotional or motivational* states will produce physiologic changes But the simple type of social interactions we have studied cannot be equated with such stimuli or be said to be linked to such kinds of emotional states The physiologic effects *of social* and/or tactual contact have been poorly studied, and their effects are far from well understood We can, however conclude from out past work that such stimuli often exert potent effects on the cardiovascular system Furthermore, *although* the "objective" aggregate of stimuli that comprise what we call human contact are complex it is still *possible to* document highly regular responses, as is noted in this study, and has been pointed out in our CCU observations[2-5]

Finally, one aspect of these experiments that deserves emphasis is that neither the patient nor *many of the personnel interacting with the* patients were aware they were being observed. In that sense, these data must be considered in a different light from the usual type of human experimentation in which the subject is quite aware that an experiment is being *conducted in* an environment that is clearly contrived. The overpowering reality of the clinical situation that formed the background of the observations made in this report cannot be ignored it was one of life and death

As has been emphasized in our previous reports it also seems that clinical personnel by their mere presence, can significantly change the cardiac system they may be attempting to monitor

Summary

This study examines the effects of human contact on the heart rate of four seriously injured patients who were on d tubocurarine *and ar*tificially respirated All four patients showed significant heart rate changes during routine clinical interactions such as pulse taking or when a nurse held their hand and comforted *them* Coupled with previous animal and *human obser*vations, these findings indicate that human contact can serve as a potent stimulus for change in cardiovascular functioning of other humans These studies also indicate that heart reactions to human contact *(1) occur in patients* where musculoskeletal movements are blocked and who are respired regularly (2) occur even in the context of intense sensory bombardment, (3) can be of a magnitude equivalent *to* such strong physi*cal stimuli as tracheal suction* and (4) can occur even when the patients are described as unconscious and comatose

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Diagnostic value of Q-waves in inferior myocardial infarction

U R Shettigar, M B B S
Herbert N Hultgren, M D F A C C
James F Pfeifer M D
Martin J Lipton M D
Palo Alto Calif

The existence of a high correlation between abnormally wide Q waves and healed myocardial infarction is well known Previous work of Wilson and co workers,[1] Pardee,[2] Fenichel and Kugel,[3] Myers and co workers [4] and Goldberger[5] established the theoretical and empirical basis for the association between abnormal Q waves and myocardial scars Q wave criteria for the diagnosis of myocardial infarction based on autopsy studies have also been investigated.[3,4]

In recent years since the development of cine angiographic techniques for the study of coronary arteries and left ventricular function similar correlations have been made between electrocardiographic findings and abnormalities in the coronary circulation and left ventricular contraction [6] Myocardial infarction is usually associated with total or sub total occlusion of the coronary artery supplying the infarcted area of myocardium In addition the left ventricular angiogram frequently reveals contraction abnormalities of the area of infarction For example in inferior myocardial infarction the right coronary artery (RCA) is frequently totally obstructed and the inferior wall of the left ventricle contracts very poorly or may be dyskinetic or aneurysmal

Electrocardiographic diagnosis of inferior myocardial infarction is relatively easy in the acute situation since characteristic ST segment and T wave abnormalities accompany the Q waves in the inferior Leads II III, and aV_F However, not infrequently, by the time a patient sees the physician, the classical electrocardiographic features of acute myocardial infarction may not be present since the ST segment and T wave changes are transient and the evidence for myocardial infarction may be found only in the abnormalities of the QRS deflection

Healed inferior myocardial infarction frequently poses a difficult diagnostic problem for electrocardiographers since the decision as to the presence or absence of infarction rests solely on a correct evaluation of QRS deflections or Q waves in the extremity Leads II III, and aV_F. It is also the common experience of many cardiologists that the abnormal or diagnostic Q waves may be seen only in one or two of the inferior leads and some times in none of the leads About 10 per cent of patients with inferior myocardial infarction may reveal "rS pattern (an initial small r wave followed by deep S) in Leads II, III, and aV_F which in the presence of left axis deviation, may be mistakenly diagnosed as left anterior hemiblock [7]

It has been stated that the significance of a Q wave in Lead III can be evaluated by recording Lead III during deep inspiration Abnormal Q waves are believed to persist during this maneuver while benign Q waves usually disappear or become small [8] No critical and systematic investigation has been made of the value of this maneuver

The present study was carried out with the following objectives (1) to evaluate the diagnostic significance of Q waves in healed inferior myocardial infarction (2) to investigate the correlation between abnormal Q waves and contraction abnormalities of the left ventricle and (3) to

From the Veterans Administration Hospital Palo Alto

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Reprint requests to Dr Herbert N Hultgren, Chief Cardiology Service Veterans Administration Hospital 3801 Miranda Ave Palo Alto Calif 94304

Table I Tabulation of clinical data

ECG patterns of 48 patients with old IMI	Total	Associated AMI	Multi vessel disease	RCA obstruction	Inferior wall asynergy	Both RCA obstruction and inferior wall asynergy	Anterior wall asynergy
I Electrocardiographic criteria for IMI is present (diagnostic Q waves in Leads II III and aV_F or in III and aV_F)	21	3	21	21 (12 = 100%) (9 = > 80%)	16	16	6
II Electrocardiographic criteria for IMI is not present (absence of diagnostic Q waves in any of the three leads or presence in Lead III only)	27	8	26 (1 had single vessel disease)	27 (21 = 100%) (6 = > 80%)	20	20	11
All cases of IMI (combined I and II)	48	11	47	48	36	36	17

determine the value of deep inspiration in evaluating abnormal Q waves in Lead III

Methods

Hospital records of 85 patients who underwent coronary and left ventricular angiography in the last three years at Palo Alto Veterans Administration Hospital were examined for the evidence of inferior myocardial infarction All patients were men between the ages of 39 and 65 with a mean age of 52 years All the patients in the study had coronary artery disease with disabling angina pectoris and most had a clear cut history of acute myocardial infarction All were considered candidates for saphenous vein aorto coronary bypass surgery Forty eight of 85 patients had evidence of inferior myocardial infarction based on at least two of the following findings (1) clinical history of myocardial infarction substantiated by hospital records and acute electrocardiographic changes (2) total or sub total (more than 80 per cent narrowing) obstruction of the right coronary artery and (3) contraction abnormalities of inferior ventricular wall.

All 48 patients demonstrated obstruction of the right coronary artery Thirty six of these 48 patients demonstrated associated left ventricular inferior wall contraction abnormalities Twelve patients had right coronary artery obstruction no left ventricular wall asynergy but clear prior clinical and electrocardiographic evidence of acute inferior myocardial infarction Clinical and angiographic data regarding patients in the study are summarized in Table I

Electrocardiograms of the 48 patients with inferior myocardial infarction were examined for the presence or the absence of diagnostic Q waves in Leads II III and aV_F. The Q wave was considered diagnostic when it measured 0 04 second or more in duration and more than 25 per cent of the R wave amplitude

In the same group of patients the size and the distribution of diagnostic Q waves in the three limb Leads II III and aV_F was compared with the presence and extent of the left ventricular inferior wall contraction abnormalities The effect of inspiration upon the Q wave in Lead III recorded during routine electrocardiography was examined in all 48 patients

Results

Of the 85 patients with severe coronary artery disease 48 (56 per cent) had evidence of inferior myocardial infarction by the criteria cited above The results can be summarized under three headings

1 Diagnostic value of Q wave in old inferior myocardial infarction Of the 48 patients with inferior myocardial infarction only 15 per cent revealed diagnostic Q waves in all the three

Table II Distribution of diagnostic Q waves in the three extremity Leads II, III, and aV_F

Distribution of Q waves	*Number of patients*	*Per cent*
No diagnostic Q waves in Leads II III and aV_F	14	29
Diagnostic Q waves in all three leads	7	15
Diagnostic Q waves in Lead III only	13	27
Diagnostic Q waves in Leads III and aV_F only	14	29
Diagnostic Q waves in Lead II only	0	0
Diagnostic Q waves in Lead aV_F only	0	0

Table III Relative frequency of diagnostic Q waves in the respective leads

	Number of patients	*Per cent*
Diagnostic Q waves in Lead III	34	70
Diagnostic Q waves in Lead aV_F	21	43
Diagnostic Q waves in Lead II	7	15

Leads II III and aV_F (Table II) and 29 per cent (14) did not reveal diagnostic Q waves in any of the three leads Twenty seven per cent (13) had diagnostic Q waves only in Lead III and 29 per cent (14) had Q waves in both Leads III and aV_F None had diagnostic Q waves in Leads II or aV_F alone

Diagnostic Q waves were most frequent in Lead III (70 per cent) and least frequent in Lead II (Table III)

2 Correlation between inferior wall asynergy and distribution of Q waves in the diagnostic Leads II III and aV_F Seven patients with inferior myocardial infarction had diagnostic Q waves in all the three leads and all of them (100 per cent) demonstrated left ventricular inferior wall asynergy on angiography (Table IV) On the other hand of the 13 patients with inferior myocardial infarction who had no diagnostic Q waves in any of the three inferior leads, only 7 patients (54 per cent) revealed contraction abnormalities of the inferior wall

3 Value of Lead III obtained in deep inspiration as a means of distinguishing between an abnormal (diagnostic) Q3 from a normal one Of the 48 patients with confirmed inferior myocardial infarction, 25 (52 per cent) retained diagnostic Q waves on deep inspiration, while 9 (19 per cent) revealed significant diminution or total disappearance of Q waves (Fig 1) Fourteen patients (29 per cent) with confirmed inferior myocardial infarction had nondiagnostic Q waves in Lead III which remained nondiagnostic during deep inspiration (Table V)

Discussion

Most previous studies correlating the electrocardiogram with healed infarction have been based on autopsy data Such studies have the advantage of a clear diagnosis of the presence size and distribution of the myocardial scar as well as direct observation of the associated coronary arterial disease

The present study is based upon indirect evidence of the presence and distribution of healed myocardial infarction and lacks the precision of evaluation of myocardial scarring that can be attained in autopsy studies However the object of the present study was not to relate scar size and distribution to the electrocardiogram but to evaluate the electrocardiogram signs in patients who had proved inferior myocardial infarction Proof of inferior myocardial infarction consisted of the presence of prior acute electrocardiogram changes in 12 patients total or sub total right coronary artery obstruction in 48 patients, and inferior wall contraction abnormalities in 36 patients These criteria are probably highly reliable when at least two of the three criteria are present One criteria alone may not be diagnostic

Another possible limitation of the present study is that all of the patients had disabling angina and, therefore most of the patients had obstructive disease of the left anterior descending or left circumflex vessels as well Seventeen of 48 patients had anterior wall asynergy and 11 out of 48 patients had electrocardiographic evidence of prior anterior infarction The effect of these features upon the electrocardiographic signs of inferior infarction are not known but must be considered This should be determined in a group of patients with only inferior infarction

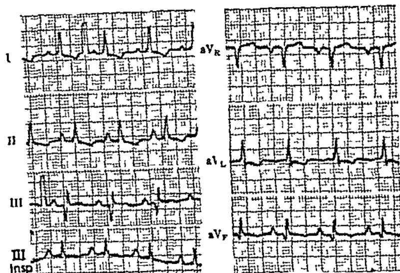


Fig 1 A 48 year-old patient with a history of myocardial infarction and disabling angina pectoris revealed total occlusion of right coronary artery and hypokinesia of inferior wall of left ventricle on angiographic studies. Note disappearance of abnormal Q_3 on inspiration.

Table IV Correlation between left ventricular inferior wall asynergy and distribution of diagnostic Q waves in Leads II III and aV_F in confirmed cases of IMI

Q wave distribution in Leads II, III and aV_F	*Total No. of patients*	*No of patients revealing inferior wall asynergy*	*Correlation (%)*
Diagnostic Q waves in Leads II III and aV_F	7	7	100
Diagnostic Q waves in none of the leads	13	7	54

and without electrocardiographic or angiographic evidence of anterior myocardial infarction. In the present study 21 patients fell into this category Their data were not substantially different from patients with anterior myocardial infarction.

Massie and Walsh[9] in their study of 45 patients with inferior myocardial infarction noted that diagnostic Q waves present in Lead III alone in 20 per cent of patients in Lead III and aV_F in 24 per cent, in all leads in 12 per cent and no diagnostic Q waves in all three leads in 36 per cent These figures are fairly close to what we found in our study

As evident from our studies Lead III revealed diagnostic Q waves in about two thirds of the patients with inferior myocardial infarction and Lead aV_F was found to be the next most sensitive lead. Although this seems to imply that Lead III is the lead of diagnostic preference in inferior myocardial infarction this is not entirely true for Lead III is more prone than either of the two leads to yield false positive interpretation of infarction Massie and Walsh[9] found 4 per cent of electrocardiograms of normal persons reveal abnormal Q waves in Lead III Besides Lead III and less commonly Lead aV_F may reveal abnormal Q waves in chronic obstructive lung disease cor pulmonale right bundle branch block and occasionally in left ventricular hypertrophy From an overall standpoint both of diagnostic sensitivity and reliability Lead aV_F is probably the preferred diagnostic lead in inferior myocardial infarction [9]

Replacement of contractile tissue or myocardium by scar tissue as is the case in myocardial infarction results in contraction abnormalities of the particular segment of the heart involved. A significantly large mass of myocardium should

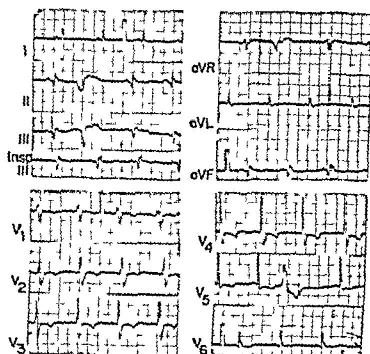


Fig 2 A 61 year old patient with a history of myocardial infarction and severe angina pectoris revealed total obstruction of right coronary artery and akinetic inferior wall of left ventricle on angiographic studies Note persistence of diagnostic Q_3 on inspiration an indication of inferior myocardial infarction according to Lyle However the diagnosis of inferior myocardial infarction was never in doubt since diagnostic Q waves were also seen on Leads II and aV_F

Table V Q wave changes in Lead III upon deep *inspiration as noted in 48 confirmed cases of* IMI

Q_3 changes with inspiration	*Number of patients*	*Per cent*
Diagnostic (abnormal) Q_3 which remains diagnostic upon inspiration	25	52
Diagnostic Q_3 which became nondiagnostic upon inspiration	9	19
Nondiagnostic Q_3 which remains nondiagnostic on *inspiration*	14	29

be involved in order for the left ventricular asynergy to be obvious on angiography Size and the distribution of Q waves in the diagnostic leads closely correlate with size or the extent of myocardial infarction [6] It is obvious that in our study the patients who had diagnostic Q waves in all three leads had more extensive inferior wall scarring than the group of patients who had no diagnostic Q waves in any of the three leads and logically, the former group revealed 100 per cent incidence of left ventricular inferior wall asynergy as opposed to the low incidence (54 per cent) in the latter group

The question arises since deep Q waves in Lead III (Q_3) are a fairly frequent (4 per cent) finding in normal persons, is it possible to develop a method for distinguishing these from abnormal Q_3 due to inferior myocardial infarction? We, like many others have routinely used Lead III in deep inspiration in an attempt to differentiate a diagnostic Q_3 from a benign one, but so far, we have not found this technique effective to this end

Lyle[8] in 1943, first proposed the use of deep inspiration as a means of identifying abnormal Q waves in Lead III She interpreted the disappearance or diminution of Q_3 upon deep inspiration as due to positional changes and, hence indicating the benign nature of Q_3 Some investigators explained the respiratory electrocardiographic changes on the basis of positional changes of the heart but others felt that nervous and hemodynamic factors such as diastolic volume changes are involved [10,11] Simonson Nakagawa and Schmitt[12] found that QRS and T vectorial changes cannot be explained adequately *on the basis of anatomic respiratory* changes alone as there was no quantitative relationship between electrocardiographic and respiratory changes So, Lyle s assumption that disappearance of Q_3 during inspiration as due to positional changes is not proved.

Our study revealed that a significant number of patients (19 per cent) with proved inferior myocardial infarction demonstrated diminution or total disappearance of abnormal Q waves in Lead III upon deep inspiration It should also be noted that most of the 25 patients (52 per cent) with proved inferior myocardial infarction who retained an abnormal Q_3 upon deep inspiration revealed abnormal Q waves in Lead aV_F or both Leads aV_F and II and the electrocardiographic diagnosis of inferior myocardial infarction could have been made even without the benefit of this special lead or a thirteenth lead (Fig 2) [13] Unfortunately, widespread acceptance of unproved diagnostic procedure is not rare in the history of medicine Many hospitals routinely obtain Lead III in deep inspiration to evaluate Q waves in Lead III A recent survey[14] of 166 hospitals in the

upper midwest revealed that about one third employed this technique It is our conclusion that Lead III in inspiration serves no useful purpose and may lead to a false sense of security in patients with inferior myocardial infarction

Summary

Forty eight patients with proved, healed, inferior myocardial infarction were studied to determine the electrocardiographic characteristics of this syndrome the correlation between electrocardiographic abnormalities and angiographic findings and to determine the value of recording Lead III during inspiration to identify abnormal Q waves

The diagnosis of inferior myocardial infarction (IMI) was established by the presence of two of the following three criteria (1) past history of acute infarction associated with typical acute electrocardiographic changes and compatible clinical data (2) total occlusion or more than 80 per cent occlusion of the right coronary artery and (3) contraction abnormalities of the inferior left ventricular wall

Fifteen per cent of patients with inferior myocardial infarction had diagnostic Q waves in all the three limb Leads II III and aV_F and 29 per cent of patients had no diagnostic Q waves in any of the three limb leads Relative frequency of diagnostic Q waves in inferior myocardial infarction were found to be 70 43 and 15 per cent in Leads III aV_F and II respectively

One hundred per cent correlation was noted between left ventricular inferior wall asynergy and presence of diagnostic Q waves in all the limb Leads II III and aV_F, but the correlation was low (54 per cent) when none of the limb Leads II III and aV_F revealed diagnostic Q waves

Obtaining Lead III in deep inspiration to differentiate an abnormal Q wave due to inferior myocardial infarction from a benign Q wave was not found to be a reliable measure and could result in false negative diagnosis of inferior myocardial infarction in a significant number of patients

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Complete and ıncomplete revascularızatıon at aortocoronary bypass surgery Experıence wıth 392 consecutıve patıents

J Frederıck McNeer, M D *
Martın J Conley, M D
C Frank Starmer, Ph D
Vıctor S Behar, M D
Yıhong Kong, M D **
Robert H Peter, M D
Alan G Bartel, M D
H Newland Oldham, Jr , M D
W Glenn Young, Jr , M D
Davıd C Sabıston, Jr , M D
Robert A Rosatı M D ***
Durham N C

In a prevıous report,[1] we suggested that the com pleteness of myocardıal revascularızatıon may affect operatıve survıval Others[2-4] have sug gested that completeness of myocardıal revas cularızatıon may affect long term survıval as well as the degree of relıef of angınal paın Thıs report detaıls our experıence wıth the ımmedıate and long term results of 'complete" and ın complete' revascularızatıon ın 392 consecutıve patıents wıth coronary artery dısease who were evaluated and operated upon at Duke Unıversıty Medıcal Center (DUMC)

Methods

The data bank Durıng the four year perıod from August, 1969 through July 1973 1 233 pa tıents were evaluated for coronary artery dıs ease Patıents wıth coronary artery dısease who had had prıor revascularızatıon elsewhere, con genıtal heart dısease ıdıopathıc hypertrophıc subaortıc stenosıs or valvular heart dısease other than mıtral ınsuffıcıency thought to be sec ondary to ıschemıc heart dısease were not ın cluded ın these 1,233 patıents Prıor to cathe terızatıon each patıent wıth chest paın was classıfıed accordıng to the New York Heart Asso cıatıon (NYHA) functıonal class for angına[5] Each patıent was categorızed as havıng 0 1, 2 or 3 vessels wıth sıgnıfıcant dısease Sıgnıfıcant dıs ease was defıned as 70 per cent or greater occlu sıon of a major coronary artery Patıents wıth sıgnıfıcant obstructıon of the left maın coronary artery were consıdered as havıng two vessel dıs ease unless they also had a sıgnıfıcant occlusıon ın the rıght coronary artery In that case they were consıdered to have three vessel dısease Of the 1 233 patıents 878 had sıgnıfıcant dısease of at least one coronary artery Three hundred nınety two of these patıents underwent aor tocoronary bypass surgery at DUMC 17 patıents underwent ventrıcular surgery wıthout bypass 461 were treated medıcally, and eıght had sur gery elsewhere The 392 patıents upon whom thıs report was based ıncluded the 269 patıents pre vıously reported.[1] Saphenous veın bypass *from*

From the Department of Medıcıne Dıvısıon of Cardıology and the Department of Surgery Duke Unıversıty Medıcal Center

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Reprınt requests to Dr Robert A Rosatı Box 3337 Duke Unıversıty Medıcal Center Durham N C 27710

*Robert Wood Johnson Clınıcal Scholar

**Establıshed Investıgator Amerıcan Heart Assocıatıon

***Dırector Robert Wood Johnson Clınıcal Scholars Program

Table 1 Characterizing parameters prior to surgery

Sex	*Treatment prior to zero time*	*Pressures*
Age	B blockers	Right atrial mean
Weight	Nitroglycerin	Pulmonary artery diastolic
Patient status (private, staff)	Long acting nitrates	Pulmonary capillary wedge
Duration of ischemic heart disease (IHD)	Anticoagulants	Left ventricular end diastolic
Hx ischemic pain	Digitalis	Aortic systolic
Type of pain (typical angina atypical angina, non anginal)	Diuretics	Aortic diastolic
Course of pain (stable improving progressing)	Antiarrhythmics	Arteriovenous oxygen difference
Severity of pain (NYHA functional class)	*Body surface area*	Cardiac output
Precipitators of pain	*Xanthoma*	Cardiac index
Effort	*Fundoscopic examination*	Ejection fraction
Meals	*Normal precordial movement*	*Coronary anatomy*
Temperature extremes	*Localized area of chest tenderness*	Number of vessels with 70 per cent or greater occlusion
Emotional stress	*Rales*	Left main coronary artery (normal, diffuse subtotal total)
Sexual intercourse	*Atrial gallop*	Left anterior descending (normal diffuse subtotal total)
Rest	*Ventricular gallop*	Left circumflex (normal, diffuse subtotal total)
Sleeping	*Early systolic murmurs*	Right coronary artery (normal diffuse subtotal total)
Frequency of pain	*Mid systolic murmurs*	*Left ventriculogram*
Number of nitroglycerin per day	*Late systolic murmurs*	Normal
Hx myocardial infarction	*Holosystolic murmurs*	Asynergy apical
Hx arrhythmias	*Peripheral pulses*	Asynergy anterior
Hx congestive heart failure	*Peripheral bruits*	Asynergy posterior
Hx hypertension	*Fasting blood sugar*	Diffusely abnormal
Hx diabetes	*Cholesterol*	Aneurysm
Hx obesity	*Heart size chest film*	Mitral insufficiency
Hx smoking	*Electrocardiogram*	
Hx hyperlipidemia	Left ventricular hypertrophy	
Family Hx IHD	Anterior myocardial infarction	
Hx cerebrovascular disease	Diaphragmatic myocardial infarction	
Hx peripheral vascular disease	Lateral myocardial infarction	
Hx menopause	Left bundle branch block	
Hx hiatal hernia	Right bundle branch block	
Hx gallbladder disease	Nonspecific intraventricular conduction disturbances	
	Left axis deviation	
	Right axis deviation	
	Resting ST T wave changes	
	Exercise test (positive negative)	

Hx = history of
NYHA = New York Heart Association
Coronary arteries classified as normal diffuse = 70 per cent occluded, subtotal = 70 to 99 per cent occluded, and total = 100 per cent occluded.

the ascending aorta to the involved coronary artery(s) was performed using cardiopulmonary bypass mild hypothermia induced electrical fibrillation and intermittent aortic cross clamping[1]

Patients were considered to have had complete revascularization only if all major coronary arteries with 70 per cent occlusion received at least one bypass graft Thus completely revascularized patients were those with three vessel disease and three or more grafts those with two vessel disease and two or more grafts and those with one vessel disease and one or more grafts. Patients were considered incompletely revascularized if any vessel with a 70 per cent or more occlusion did not receive at least one graft Thus incompletely revascularized patients were those with three vessel disease and graft(s) to one or two vessels or those with two vessel disease and graft(s) to only one vessel

Surgical mortality included all patients who died between induction of anesthesia and hospital discharge Follow up data including life death status and NYHA functional class for angina were obtained at 6 12 and 24 months postoperatively These data were obtained by a

Table II Total group survival (%)

	'Complete revascularization*	χ^2 p value	Incomplete revascularization†
Survive surgery	168/186 (90%)	0 9 NS	180/206 (87%)
Six month survival	156/174 (90%)	2 5 NS	158/188 (84%)
Twelve month survival	136/154 (88%)	3 6 NS	123/153 (80%)
Twenty four month survival	71/86 (83%)	1 4 NS	67/89 (75%)

Complete revascularization three vessel disease with three grafts two vessel disease with two or three grafts one vessel disease with one or two grafts

† Incomplete revascularization three vessel disease with one or two grafts two vessel disease with one graft.

Table III Total group relief of anginal pain (%)

	'Complete' revascularization*	χ^2 p value	Incomplete" revascularization†
Six month interval			
Pain free	113/153 (74%)		97/151 (64%)
Improved 2‡	9/153 (6%)	4 78 NS	15/151 (10%)
Improved 1§	6/153 (4%)	(DF=3)	12/151 (8%)
No improvement¶	25/153 (16%)		27/151 (18%)
Twelve month interval			
Pain free	87/133 (65%)	3 35 NS	70/120 (58%)
Improved 2	11/133 (8%)	(DF=3)	15/120 (13%)
Improved 1	10/133 (8%)		15/120 (13%)
No improvement	25/133 (19%)		20/120 (16%)
Twenty four month interval			
Pain free	39/73 (55%)		32/60 (53%)
Improved 2	4/71 (6%)	1 64 NS	7/60 (12%)
Improved 1	6/71 (8%)	(DF=3)	4/60 (7%)
No improvement	22/71 (31%)		17/60 (28%)

Complete revascularization three vessel disease with three grafts two vessel disease with two or three grafts one vessel disease with one or two grafts

† Incomplete revascularization three vessel disease with one or two grafts two-vessel disease with one graft.

‡Improve 2 improvement by two NYHA functional classifications for anginal pain but not pain free

§Improve 1 improvement by one NYHA functional classification for anginal pain but not pain free

¶ No improvement NYHA functional classification for anginal pain the same or worse

staff cardiologist during a clinic visit or by a research associate by telephone The follow up data were 99 5 per cent complete

All data were contained in our previously described coronary artery disease data bank [6] Analyses were performed using an interactive data analysis system [7 8]

Data analysis The 'completely' revascularized cohort contained 186 patients (48 per cent of the population) There were three patients with one vessel disease who received two bypass grafts and six patients with two vessel disease who received three bypass grafts All other 'completely' revascularized patients had one graft to each significantly diseased vessel The 'incompletely' revascularized cohort contained 206 patients (52 per cent of the population) Patients were considered to be pain free if they had chest pain prior to surgery and were NYHA functional Class I at follow up Ten patients who had not had chest pain or were Class I prior to surgery were not included in the analysis of relief of anginal pain Patients who were not pain free at follow up were described as having improved one or two NYHA functional classes or as not improved.

Survival rates were calculated as the number of patients who survived an interval divided by the total number of patients followed for that interval Relief of pain rates were calculated for survivors of each interval The survival of the completely' and 'incompletely revascularized cohorts was compared postoperatively and at 6 12, and 24 months using the Chi square test Relief of pain was compared at 6, 12, and 24 months using the Chi square test

The completely and incompletely' revascu

Table IV Presurgery inequalities in total population

	Prevalence (%)	
	Completely revascularized	Incompletely revascularized
History of previous myocardial infarction	43	58
History of CHF	8	20
Positive exercise test	48	59
History of diabetes	19	9
Normal contraction pattern left ventriculogram	61	39
Apical asynergy left ventriculogram	17	29
Anterior asynergy left ventriculogram	13	2[illegible]
Aneurysm left ventriculogram	0	6
Right coronary normal	10	2
Left circumflex coronary normal	35	7
Prior treatment with diuretics	10	22

larized cohorts were examined to determine the extent of baseline inequalities in 89 presurgical characteristics (Table I) Dichotomous parameters were compared using the Chi square test. Continuous parameters were compared using Student s t test Because such a large number of characteristics were tested, inequalities were considered significant at the P $<$ 0 05 level when $\chi^2 > 6\ 635$ with one degree of freedom or greater than 9 210 and 11 34 with two and three degrees of freedom respectively[9]

Patients with one vessel disease were by definition completely revascularized Because these low risk patients biased the results in the completely revascularized cohort all analyses were repeated after stratifying for number of vessels diseased. Thus survival relief of chest pain and baseline characteristics were determined and compared in completely and incompletely revascularized patients with two vessel disease and in completely and incompletely revascularized patients with three vessel disease

Results

The survival rates from the completely and incompletely revascularized cohorts is shown in Table II Though the survival rates at each interval appear higher in the completely revascularized cohort there is no significant difference in survival at any interval Table III shows the degree of relief of chest pain at each interval. Again although the completely revascularized patients appear to have experienced a greater degree of relief of chest pain the differences are not significant at any interval. When the 89 baseline characteristics of the completely and incompletely revascularized cohorts were compared, 11 baseline inequalities were found. The prevalence of these unequally distributed characteristics is shown in Table IV It can be seen that except for the prevalence of diabetes mellitus the completely revascularized cohort appears less sick than the incompletely revascularized cohort

Table V One vessel disease subgroup survival (%)

Survival time	Complete revascularization
Survive surgery	72/76 (9 ,%)
Six month	66/71 (93%)
Twelve month	60/65 (92%)
Twenty four month	35/38 (92%)

Complete re ascularization one vessel d sease with one or two grafts.

Table V shows the survival rates in patients with one vessel disease who by definition are completely' revascularized. The survival rates at each interval are higher than the survival rates of the entire completely revascularized cohort (seen in Table II)

Table VI shows the survival of the completely and incompletely revascularized cohorts with significant occlusion in two coronary vessels Seventy one patients (56 per cent) had complete revascularization and 58 patients (44 per cent) had incomplete revascularization There are no significant differences between the two cohorts in survival. Table VII shows the degree of relief of anginal pain in the completely and incompletely revascularized

Table VI Two vessel disease subgroup survival (%)

	'Complete revascularization*	X^2 p value	Incomplete revascularization†
Survive surgery	63/71 (89%)	0 0 NS	51/58 (88%)
Six month survival	60/68 (88%)	0 5 NS	46/55 (84%)
Twelve month survival	65/63 (87%)	2 2 NS	36/47 (77%)
Twenty four month survival	28/36 (78%)	0 0 NS	24/31 (77%)

Complete revascularization two vessel disease with two *or* three grafts
†Incomplete revascularization two-vessel disease with one graft.

Table VII Two vessel disease subgroup relief of anginal pain (%)

	"Complete revascularization*	X^2 p value	Incomplete revascularization†
Six month interval			
Pain free	43/58 (74%)	3 16 NS (DF=3)	31/45 (69%)
Improve 2‡	2/58 (3%)		4/45 (9%)
Improve 1§	2/58 (3%)		4/45 (9%)
No improvement¶	11/58 (20%)		6/45 (13%)
Twelve month interval			
Pain free	31/53 (59%)	2 05 NS (DF=3)	21/35 (60%)
Improve 2	2/53 (4%)		3/35 (9%)
Improve 1	4/53 (7%)		4/35 (11%)
No improvement	16/53 (30%)		7/35 (20%)
Twenty four month interval			
Pain free	17/28 (61%)	1 99 NS (DF=3)	11/22 (50%)
Improve 2	1/28 (4%)		3/22 (14%)
Improve 1	2/28 (7%)		1/22 (4%)
No improvement	8/28 (28%)		7/22 (32%)

Complete revascularization two-vessel disease with two *or* three grafts.
†Incomplete revascularization two vessel disease with one graft.
‡Improve 2 improvement by two NYHA functional classifications for anginal pain but not pain free
§Improve 1 improvement by one NYHA functional classification for anginal pain but not pain free
¶ No improvement NYHA functional classification for anginal pain the same or worse

cohorts There are no significant differences in relief of anginal pain None of the 89 baseline characteristics are unequally distributed

The comparison of the survival rates of ' com pletely' and 'incompletely revascularized co horts in the subgroup with significant occlusion in all three coronary vessels is seen in Table VIII Thirty nine patients (21 per cent) had 'com plete' revascularization and 148 patients (79 per cent) had ' incomplete' revascularization There are no significant differences in survival The comparison of relief of anginal pain in the com pletely' and ' incompletely' revascularized co horts is shown in Table IX There are no signifi cant differences in relief of anginal pain None of the baseline characteristics are unequally dis tributed between the "completely and "in completely ' revascularized cohorts

Discussion

The experience in our total group as well as in subgroups with two or three vessel disease with respect to complete or 'incomplete revascularization reveals no significant dif ferences in survival or relief of anginal pain at each interval Apparent percentage differences created by inclusion of patients with one vessel disease in the total group disappear or decrease when the population is stratified by the number of vessels diseased The inequalities in baseline characteristics demonstrated in the total popula tion also disappear on comparison of subgroups stratified for the number of vessels diseased.

Other data[1,4] have been interpreted as imply ing 'that the hazards of increased pump time re quired for multiple grafts are offset by the decreased likelihood of operative and postopera

Table VIII Three vessel disease subgroup survival (%)

	"Complete revascularization*	X^2 p value	"Incomplete" revascularization
Survive surgery	33/39 (85%)	0 2 NS	129/148 (87%)
Six month survival	30/35 (85%)	0 1 NS	112/133 (84%)
Twelve month survival	21/26 (81%)	0 0 NS	90/110 (82%)
Twenty four month survival	8/12 (67%)	0 3 NS	43/58 (74%)

Complete re ascularization three v ssel diseas with three grafts
†Incompl t revascularization three v ssel disease with one or two grafts

Table IX Three vessel disease subgroup relief of anginal pain (%)

	Complete" revascularization*	X^2 p value	"Incomplete" revascularization†
Six month interval			
Pain free	21/29 (72%)		66/106 (62%)
Improve 2‡	3/29 (10%)	1 37 NS	12/106 (11%)
Improve 1§	.../29 (8%)	(DF=3)	8/106 (8%)
No improvement¶	3/29 (10%)		20/106 (19%)
Twelve month interval			
Pain free	15/21 (71%)		49/85 (58%)
Improve 2	2/21 (10%)	2 24 NS	12/85 (14%)
Improve 1	3/21 (14%)	(DF=3)	11/85 (13%)
No improvement	1/21 (5%)		13/85 (15%)
Twenty four month interval			
Pain free	3 8 (37%)		22/39 (56%)
Improve 2	2/8 (25%)	1 76 NS	4/39 (10%)
Improve 1	1/8 (12%)	(DF=3)	3/39 (8%)
No improvement	2/8 (25%)		10/39 (26%)

Complete re ascularization t ree vessel disea with three grafts
†Incomplete revascularization three essel disease with one or two grafts
‡Imp ove 2 improvem nt by two NYHA funct onal classifications for anginal pain but not p in free
§Improve 1 mpro ment by one NYHA functional cl ss fic t on for anginal p n but not pa n free
¶No mprovement NYHA functional classification fo anginal pain the same or worse

tive infarction in ischemic areas [10] Some authors[1 3 4] included patients with one vessel disease in their completely revascularized population Patients with one vessel disease are low risk They have higher survival rates than patients with two and three vessel disease (Table V) They make the completely revascularized cohort appear less sick with regard to preoperative characteristics (Table IV) When survival and relief of pain rates are examined, it appears that differences are due to complete versus incomplete revascularization when in fact the differences are due to the patients with one vessel disease Per cent differences which were not statistically different were also reported.

A report from this institution[1] that included the first 269 patients in the present series described a 6 per cent (92 per cent vs 86 per cent) difference in surgical survival of completely versus incompletely revascularized patients. This observed difference was not statistically significant at that time ($x^2 = 2\ 59$ $p > 0\ 10$) and has become less significant since inclusion of the next 123 patients ($x^2 = 0\ 91$ $p > 0\ 25$) Comparison of complete and incomplete revascularization in patients with two vessel disease and in patients with three vessel disease shows the survival rates are the same regardless of the completeness of revascularization Mitchell and coworkers[2] reported a 14 per cent difference (5 of 33 vs 8 of 28) in survival in comparing patients with three vessel disease with respect to complete and incomplete revascularization This difference is not significant by Chi square analysis ($x^2 = 1\ 6$ $p > 0\ 10$) Moreover there were no deaths (0 per cent) in 8 incompletely revascu

Table VI Two vessel disease subgroup survival (%)

	Complete revascularization*	χ^2 p value	Incomplete revascularization†
Survive surgery	63/71 (89%)	0 0 NS	51/58 (88%)
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Twelve month survival	55/63 (87%)	2 2 NS	36/47 (77%)
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Complete revascularization two vessel disease with two or three grafts
†Incomplete revascularization two vessel disease with one graft.

Table VII Two vessel disease subgroup relief of anginal pain (%)

	Complete revascularization*	χ^2 p value	Incomplete revascularization†
Six month interval			
Pain free	43/58 (74%)	3 16 NS (DF=3)	31/45 (69%)
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Twelve month interval			
Pain free	31/53 (59%)	2 05 NS (DF=3)	21/35 (60%)
Improve 2	2/53 (4%)		3/35 (9%)
Improve 1	4/53 (7%)		4/35 (11%)
No improvement	16/53 (30%)		7/35 (20%)
Twenty four month interval			
Pain free	17/28 (61%)	1 99 NS (DF=3)	11/22 (50%)
Improve 2	1/28 (4%)		3/22 (14%)
Improve 1	2/28 (7%)		1/22 (4%)
No improvement	8/28 (28%)		7/22 (32%)

Complete revascularization two-vessel disease with two or three grafts
†Incomplete revascularization two-vessel disease with one graft.
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The comparison of the survival rates of 'completely and incompletely" revascularized cohorts in the subgroup with significant occlusion in all three coronary vessels is seen in Table VIII Thirty nine patients (21 per cent) had 'complete' revascularization and 148 patients (79 per cent) had 'incomplete' revascularization There are no significant differences in survival The comparison of relief of anginal pain in the completely' and incompletely revascularized cohorts is shown in Table IX There are no significant differences in relief of anginal pain None of the baseline characteristics are unequally distributed between the "completely' and "incompletely" revascularized cohorts

Discussion

The experience in our total group as well as in subgroups with two or three vessel disease with respect to complete or incomplete revascularization reveals no significant differences in survival or relief of anginal pain at each interval Apparent percentage differences created by inclusion of patients with one vessel disease in the total group disappear or decrease when the population is stratified by the number of vessels diseased The inequalities in baseline characteristics demonstrated in the total population also disappear on comparison of subgroups stratified for the number of vessels diseased

Other data[1,4] have been interpreted as implying "that the hazards of increased pump time required for multiple grafts are offset by the decreased likelihood of operative and postopera

The left parasternal lift in tricuspid incompetence

T G Armstrong MD FRCP
M S Gotsman MD FRCP FACC
Durban, Natal, South Africa

A left parasternal lift is usually attributed to right ventricular hypertrophy

In a previous communication [1] we have shown that the high amplitude late systolic lift of the left parasternal region which occurs in severe mitral incompetence (MI) is due to systolic enlargement of the left atrium (Fig 6 C)

As a logical follow up to these studies we have now investigated the high amplitude left parasternal lift in severe tricuspid incompetence (TI) to define its precise character There are several good descriptions of the precordial movement in TI [2-4] but these are not widely known

The object of this paper is to draw attention to the clinical importance of bedside observation by combined palpation and auscultation of the chest wall We hope *to show that* the left parasternal lift of severe TI is of high amplitude diastolic in time and has its peak on or about the first heart sound. On the other hand the lift of right ventricular hypertrophy is *systolic in time as* is the left atrial lift of mitral incompetence The instrumental tracings shown are designed only to validate the bedside findings which we consider to be valuable diagnostic pointers

Material and methods

The phonocardiograms and records of patients with a left parasternal lift who *presented themselves* during a three year period were analyzed Four groups of patients who did not have MI were investigated and their diagnosis was confirmed by cardiac catheterization or surgery (Table I)

Kinetocardiograms (KCG) were made on a three channel direct writing recorder (Cardiopan Liechti) which used a capacitance displacement transducer with a frequency response of 10 to 170 CPS and a time constant of more than 1 2 seconds Recordings were made in different positions of the chest wall but in particular at the left sternal edge in the *position* K24 (V) and at the apex K45 or K55 The notation is given by numerals the first indicates the electrocardiographic V position and the second the intercostal space Jugular venous tracings (JVP) right parasternal and liver tracings were also recorded in certain cases The paper speed was 50 to 100 mm per second.

In addition recordings were made on a Sanborn Photographic Twin Beam recorder with a Hewlett Packard 21050B microphone and 1506A heart sound amplifier with a signal splitter to permit simultaneous registrations of low frequency left parasternal phonocardiograms (PCG) and KCG The frequency response of the displacement microphone and recorder was 0 02 to 2 000 CPS and the time constant was 50 seconds The paper speed was 75 mm per second. ECG s PCG s and KCG s were recorded simultaneously in held expiration In patients presenting with mitral disease and tricuspid incompetence recordings were made before and after replacement of the mitral valve

Methods of analysis On palpating the normal chest wall at the K24 position no heave or lift is apparent A wave form is however readily recordable The normal tracing at K24 is a brief and small outward peak at the time of the first heart sound. This is followed immediately by *retraction* which continues up to and beyond the second sound There is then a rise from the 0 point to a flat or gently rising plateau ending with a small a wave (Fig 1) [4]

From the Cardiac Unit, Wentworth Hospital, and the University of Natal, Durban South Africa

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Reprint requests to Dr T G Armstrong Wentworth Hospital, P B J ba, Natal South Africa

larized patients with two vessel disease and two deaths (8 per cent in 25 completely revascularized patients Reul Morris, and Howell[3] reported that a higher percentage (42 per cent vs 31 per cent) of patients without fatal and nonfatal complications were "completely revascularized However, 102 patients with one vessel disease were included in the completely revascularized subgroup This difference is not significantly different ($\chi^2 = 2.8$ $p > 0.05$) Paradoxically, when completely' and 'incompletely" revascularized patients with three vessel disease are analyzed, more patients with fatal and nonfatal complications had been 'completely' revascularized ($\chi^2 = 4.39$, $p < 0.05$) Comparison with respect to 'completeness of revascularization in patients with two vessel disease revealed no difference in 'completely" and incompletely revascularized patients Sheldon and co workers[4] reported greater relief of anginal pain in a 'completely revascularized subgroup of 279 patients No statistical tests were performed and the data were presented as percentages without revealing the number of patients completely and incompletely' revascularized and the number of patients in each NYHA class for angina Patients with one vessel disease were included in this analysis

The data in this report indicate that complete' revascularization is not closely coupled to survival or relief of anginal pain It remains important to attempt to define more homogenous subgroups in which 'complete revascularization may indeed be of significant value in both survival and relief of angina One also must recognize that this experience is only that through 24 months postoperatively and that with 48 month 60 month or 120 month follow up significant differences may appear In summary our experience in a group of 392 consecutive patients treated with aortocoronary bypass surgery has been examined with respect to complete' and 'incomplete' revascularization at surgery No significant difference in survival or relief of anginal pain was demonstrated by 24 months

Summary

This report presents our experience with complete" and incomplete' revascularization in 392 consecutive patients undergoing aortocoronary artery bypass surgery Patients were considered to have had complete revascularization only if all major coronary arteries with 70 per cent occlusion received at least one bypass graft. Patients were considered incompletely' revascularized if any vessel with a 70 per cent or more occlusion did not receive at least one bypass graft. The 'completely" revascularized cohort contained 186 patients and the 'incompletely" revascularized cohort contained 206 patients. The survival of the completely' and incompletely" revascularized cohorts was compared postoperatively and at 6, 12, and 24 months using the Chi square test Relief of anginal pain rates were compared at 6 12 and 24 months using the Chi square test Analyses were repeated after stratifying for number of vessels diseased The subgroup with one vessel diseased was by definition, 'completely revascularized No significant difference in survival or relief of anginal pain was demonstrated in the total group or in subgroups with 2 and with 3 vessels diseased The data indicate that 'complete revascularization is not closely coupled to two year survival or relief of anginal pain

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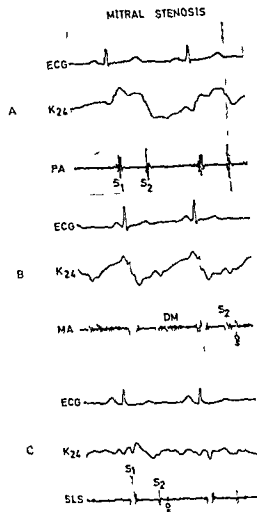


Fig 2 K24 tracings in proved mitral stenosis without TI Low amplitude and just palpable *A* Sustained outward thrust duration 340 milliseconds ratio ·/1 *B* Near normal graph duration 40 milliseconds ratio 2/13 C Nonspecific graph less than normal systolic retraction

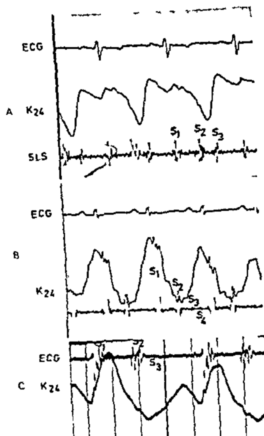


Fig 3 K24 tracings in right ventricular hypertrophy with TI. *A* Thromboembolic pulmonary hypertension Systolic retraction note rapid outward movement rapid filling wave (RFW) from 0 point to right ventricular third sound duration 40 milliseconds ratio 3/20 *B* Bilharzial pulmonary hypertension Systolic retraction note rapid rise to peak at S_1 with inflexion at S_3 duration 40 milliseconds ratio 4/25 *C* Thromboembolic pulmonary hypertension Systole dominated by retraction S_3 on slight inflection on RFW peak at S_1 preceded by halt, duration 160 milliseconds ratio 10/20

menger VSD had a right ventricular pressure at systemic level

The remainder of this group consisted of 16 patients with pure mitral stenosis proved at operation who had no mitral incompetence or tricuspid valve disease They had isolated right ventricular hypertrophy and additional pulmonary arterial hypertension (Figs 2 *A B* and *C*) The 20 patients showed a small unimpressive left parasternal lift always systolic which although palpable was seldom visible Even in patients with pulmonary stenosis and extreme right ventricular hypertrophy the systolic lift was of small amplitude and much smaller than expected for so powerful a ventricle (Fig 5) The systolic lift in mitral stenosis was slight and unremarkable in 18 out of the 20 cases, but was shown instrumentally always to have a wave form. It was sustained beyond 200 msec in 13 cases. Table II shows agreement with the results of Eddleman in 80 per cent of cases of pure RVH without TI

In a single case of mitral stenosis the systolic lift was of high amplitude and easily visible

2 Pure RVH with TI (13 cases) To palpation and vision the lift was of high amplitude in all cases In systole the peak lift came at the normal time of the first sound in 12 cases Table II shows agreement with the results of Eddleman for volume overload in 70 per cent of the cases

In diastole two patterns emerged.

In the first group of four patients (Fig 3 *A*)

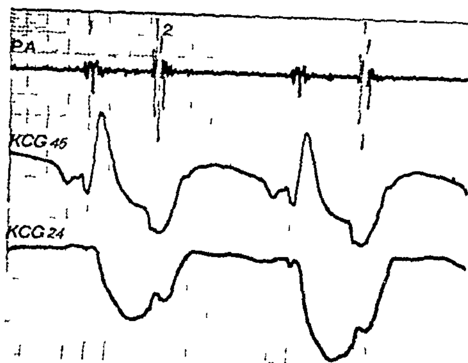


Fig 1 Normal kinetocardiogram Lowest tracing shows a normal K24 graph at V_2 position in fourth left interspace Reference tracings middle apical KCG top phonocardiogram

Table I Patients

		Cases
I	*Right ventricular hypertrophy only no TI*	20
	(a) Right heart disease	
	Severe pulmonary stenosis	3
	VSD with severe pulmonary hypertension	1
	(b) Pure mitral stenosis	16
II	*Right ventricular hypertrophy with TI*	13
	Pulmonary stenosis	2
	Pulmonary thromboembolism	3
	Primary pulmonary hypertension	2
	Bilharzial pulmonary hypertension	1
	Ebstein s syndrome	1
	Cardiomyopathy	1
	Mitral stenosis	3
III	*Postmitral valve replacement and TI*	13
IV	*Atrial septal defect*	5
	With normal pulmonary artery pressure	

We used two different methods to assess the tracings First, qualitative visual inspection second, more precise measurement of the duration of outward displacement and the ratio of outward displacement to retraction Systolic curves and impulses were divided into two groups (1) an outward systolic impulse which was often impalpable and which was sustained (Fig 2 A) or of short duration (Fig 2 C) and (2) systolic retraction which was normal (Fig 2 B)

Diastolic curves were assessed as showing (1) a very early filling wave leading to a right ventricular third sound (Fig 3 A) (2) a continuous rapid rise from 0 point to dominant a wave (Fig 3, B) and (3) intermission in the outward thrust (Fig 3 C)

Additional quantitative assessments were made using the method of Eddleman and Duke Thomas[5] (Fig 4) In pressure loaded right ventricles following the initial activation upstroke a second upstroke occurred after a shallow retraction The first upstroke divided by the small retraction, gave a ratio of more than unity and with the second outward thrust indicated pressure overload

In normal and volume loaded ventricles as in atrial septal defect (ASD) without pulmonary hypertension, a second outward thrust was not seen The ratio then became the initial out thrust divided by the total systolic retraction and was always less than unity We have called this the ratio of Eddleman We also measured the duration of outward thrust from its zero point to its return to the base line

Results

1 Pure right ventricular hypertrophy without tricuspid incompetence (20 cases) Among them were four patients all catheterized three of whom had severe pulmonary stenosis without tricuspid incompetence One had a peak systolic gradient of 200 mm Hg The fourth an Eisen

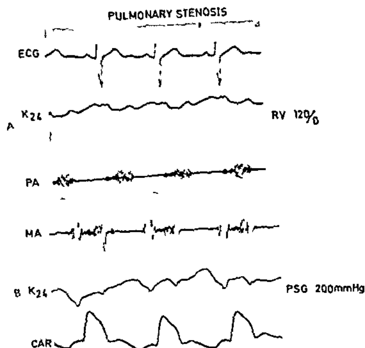


Fig 5 K24 in severe pulmonary stenosis without TI. Both left parasternal lifts were barely palpable Unimpressive diastolic filling *A*, systolic retraction RV pressure 120/0 mm. Hg *B*, small but sustained lift, 280 milliseconds, peak systolic gradient 200 mm Hg

load in all cases This systolic retraction is seen in normal persons but is usually not so deep In patients with TI outward movement was steep in diastole with a rapid filling wave even in those patients in atrial fibrillation Eight patients had a right ventricular third sound. Diastole culminated in the a wave thus producing a trough and peak appearance the nadir being at the 0 point and the peak clinically palpable at the first heart sound.

4 **Atrial septal defect (ASD)** There were five cases of secundum ASD all with normal pulmonary artery pressures. All had high amplitude palpable and visible lifts All had K24 tracings (Figs 7 A and *B*) with a sharp and continuous rapid filling wave to the a wave followed by a prominent RV activation peak The duration of this final peak was brief the outward movement being only 70 to 100 msec in all The ratio of Edleman was less than unity in all five cases The peak to the end of ejection showed a continuous decline without outward movement The general appearance of these graphs was very similar to those of the postoperative patients with TI (Figs 6 *A B* and *C*)

Discussion

Dressler[2] first described the pulsations of the chest wall in tricuspid incompetence He emphasized the presence of systolic retraction and of a rock from the left to the right side of the chest. Muller and Shillingford[6] showed that the flow in the atrium and great vessels is reversed in systole by the action of the right ventricle and that inflow into the heart must take place at greater speed in diastole This is well reflected in the movements of the chest wall at K24 Dressler[2] observed the right ventricular third sound but called it a reduplicated second sound and compared TI with constrictive pericarditis He mentioned the rock of the whole precordium from left to right in systole and particularly remarked on the rocking from the apex to the liver This we have also seen Although fully aware of the rapid right ventricular filling his main description of the physical findings was a systolic retraction of the left side of the chest

Boicourt Nagle and Mounsey[3] in a paper on the clinical significance of systolic retraction of the apical impulse mentioned adhesive pericarditis and TI as the main causes and commented

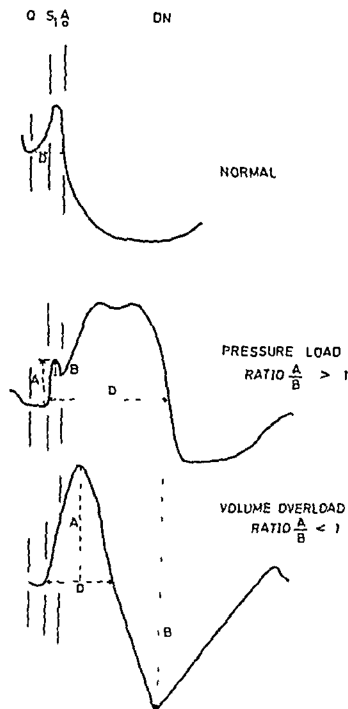


Fig 4 Schematic drawing after Eddleman and Duke Thomas *A* Normal K24 graphs *B*, RV pressure overload *C*, RV volume overload S_1 First heart sound $\frac{A}{o}$ aortic opening DN dicrotic notch D duration and $\frac{A}{B}$ ratio

there was an extremely rapid filling wave (RFW) immediately following the 0 point leading to a peak or shoulder coincident with a right ventricular third sound Following this was a long flat plateau This was followed by systolic retraction The general picture was a caricature of normal a plateau curve with a dip in systole The striking feature was the early RFW after which outward movement ceased

Table II Ratio and duration of outward movement

	Ratio			Duration	
	Total	> 1	< 1	200	200 or less
RVH without TI		80%	20%	80%	20%
No of patients	20	16	4	16	4
RVH with TI		30%	70%	30%	70%
No of patients	13	4	9	4	9
Postoperative TI			100%		100%
No of patients	13	0	13	0	13
ASD (normal PAP)			100%		100%
No of patients	5	0	5	0	5

The ratio is that of systolic outward movement to retraction. The duration of outward movement is in milliseconds. It will be seen that the majority of patients with TI have a ratio and duration similar to that of ASD with normal pulmonary artery pressure i e. volume over load. PAP = pulmonary artery pressure

The second group showed a more or less continuous and rapid movement from the 0 point to a climax at the a wave and a further rise which coincided with ventricular contraction at the first heart sound (Figs 3, *B* and *C*) A third heart sound was often seen at an inflection on the K24 upstroke (Figs 3 *B* and *C*) Sometimes there was a halt in the lift in mid diastole (Fig 3, *C*), but the upstroke was rapid before and after the halt The a wave was nearly always prominent except in patients in atrial fibrillation

3 Patients with resolving TI following surgical replacement of the mitral valve (14 cases) These patients were considered to be of special interest as their tricuspid incompetence was uncomplicated by other dynamic factors They were investigated within several days of operation and had a significant jugular v wave on which the diagnosis of TI was made One patient had had both mitral and tricuspid valves replaced The mitral valve was competent but the tricuspid valve showed a severe peri prosthetic leak at catheterization Amplitudes of the left parasternal lift were low and invisible in 10 patients and high and visible in 4 patients Seven patients were in atrial fibrillation

In systole there was a sharp outward movement at the time of the first sound due to ventricular contraction and then a steep retraction and later gentler recession continuing until the end of ejection (Figs 6 *A B* and *C*) The duration of the outward thrust and the ratio of Eddleman resembled the picture of volume over

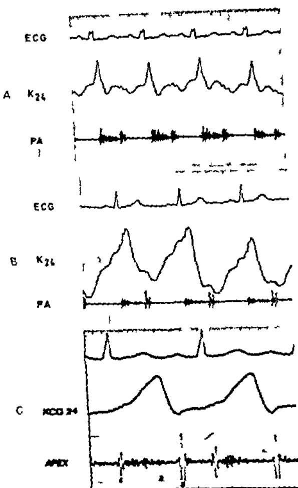


Fig 7 *A* and *B* Secundum ASD with normal pulmonary artery pressure Note resemblance to TI *A* and *B* duration 100 milliseconds. *A* ratio = 12/18 *B* ratio = 5/30 *C* Left atrial lift. Note late systolic peak at S_2 falling precipitously to S_3

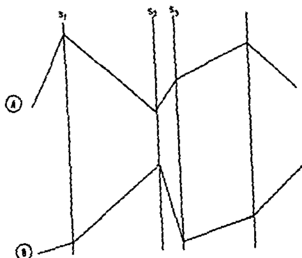


Fig 8 A and B See text

right ventricular third sound. The same picture but without the third heart sound, was seen in all of five cases of ASD without pulmonary hypertension Such high amplitude parasternal lifts were very rare in pressure loaded right ventricles and were always systolic in timing

These findings agree closely with those of Eddleman and Duke Thomas[5] who described the different KCG patterns in pressure and volume loaded right ventricles with special reference to ASD Table II shows that our findings in ASD and in pure RVH without TI agree with theirs in the majority of cases. We feel that this validates our observations and that the finding of graphs in TI similar to those in ASD strongly suggests that the contour of the graphs is determined by volume overload. The rapid and ill sustained outward thrust is due to rapid filling and equally rapid deflation of the right ventricle through the tricuspid leak

It is suggested that in TI the volume and speed of RV filling are increased by the regurgitant fraction Equally the volume ejected in systole is much greater than normal as it includes the regurgitant fraction Both these factors will increase the speed and amplitude of RV volume changes and lead to a high amplitude lift.

The right ventricle underlies the left parasternal region and movements of this part of the thoracic cage are most often caused by right ventricular events Rapid filling of the right ventricle will produce much movement of the left parasternal area and is one of the more common causes of a high amplitude lift Of the causes of very rapid right ventricular filling TI is the most common others are ASD and, less commonly ventricular septal defect We suggest that the positive outward movement in these conditions is due to rapid ventricular filling finally enhanced by the a wave

The timing is crucial in differential diagnosis. Fig 8 *A* shows the lift due to a typical rapid filling and emptying of the right ventricle in TI The peak is at the first heart sound.

Fig 8 *B* shows its antithesis in the left atrial lift The peak outward movement comes with maximal atrial expansion from left ventricular contraction at the end of ejection at the second heart sound.

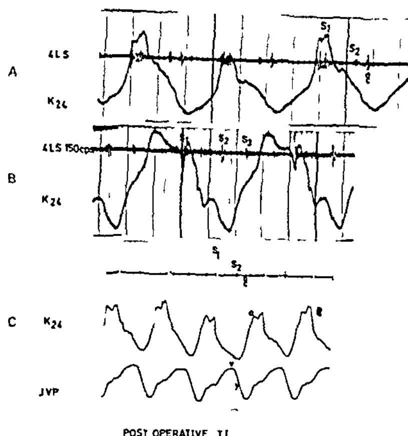


Fig 6 Postoperative TI All showed high amplitude lifts *A* Starr Edwards mitral and tricuspid valve replacement tricuspid peri prosthetic leak duration 160 milliseconds ratio 13/20 *B* Note S_3 at inflexion on upstroke duration 80 milliseconds ratio 6/22 *C* Note see saw relationship of K24 and JVP tracings peak at S_1 duration 60 milliseconds ratio 3/23

on the systolic rocking movement from the apex to the right subclavian region in patients with TI *without ventricular hypertrophy* We have also noticed this in venous and right chest wall tracings which represent the same phenomenon (Fig 6, *C*)

We have previously shown that the left parasternal lift provides a typical and diagnostic picture in severe mitral incompetence (Fig 7 *C*) [1] Its characteristics are its high amplitude and its early rise at the first sound reaching a peak at the second and then falling precipitously to the third sound

By contrast, in severe TI, whether caused by right heart disease or found as a known single valvular lesion following mitral valve replacement the parasternal lift is diastolic in timing with a peak *close to the time of the first heart* sound The lift then falls away rapidly during systole (systolic retraction) This systolic retraction has been described by a number of authors in the past and is no new observation However during examination, an outward thrusting lift impresses itself much more forcibly on the examiner than a negative retraction This *forceful* diastolic outward parasternal movement in TI is of important diagnostic help in particular because of its high amplitude

Right ventricular pressure overload usually produces a nearly invisible systolic lift of low amplitude which is well sustained throughout systole Often no palpable lift can be felt although first and second sounds are easily palpable In patients with severe right heart disease without TI Figs 2 and 5 show left parasternal lifts which were quite negligible to palpation Though often invisible their wave form was easily recorded by suitable amplification This may however, produce a false impression of *amplitude*

In strict contrast the lifts of the left atrium and of severe tricuspid incompetence are easily visible and of high amplitude MI is associated with a *systolic lift*, TI with a *diastolic lift* and a

Experimental and laboratory reports

Conduction defects in experimental atrial arrhythmia

Patrick R Montgomery M D
Peter E Dresel Ph D
Winnipeg Manitoba, Canada

It has long been known that early ectopic beats may initiate atrial arrhythmias. Clinical studies by continuous cardiac monitoring have shown that atrial fibrillation and other atrial arrhythmias are often preceded by premature atrial activations and that premature beats followed by arrhythmias have a shorter coupling interval than those which are not [1-4] In experimental animals electrical stimuli placed early in diastole are well known to produce atrial arrhythmias [3,5,9] and acetylcholine is known to potentiate the effects of these shocks [3,10] How shocks of near threshold strength produce arrhythmias is controversial We have studied the response of the atria to early diastolic stimuli in order to determine whether extrasystoles which result in arrhythmias are conducted in a different fashion from extrasystoles which do not Attention was given to the specialized conducting system whose long refractory period, and relative insensitivity to acetylcholine[11,12] might be of significance

Methods

Isolated dog hearts were perfused with blood from a donor dog by the technique of Alanis Gonzales and Lopez [13] as modified by Kirk and Dresel [14] The recipient hearts were obtained from mongrel 10 to 15 kilogram dogs of either sex anesthetized intravenously with Na pentobarbital (30 mg per kilogram) They were rapidly removed to cold oxygenated Krebs-Henseleit solution the pericardium and adjacent tissues were removed and the heart was perfused through the aorta In most cases the ventricles fibrillated when perfusion was begun and they were allowed to do so throughout the experiment In all cases the atria beat spontaneously at a regular rate The donor dog was anesthetized with Na pentobarbital (30 mg per kilogram) heparinized (400 units per kilogram) and respired with 100 per cent oxygen with a Palmer Ideal pump A double headed DeBakey roller pump was used to perfuse the recipient heart with blood from the carotid artery Perfusion pressure was 100 mm Hg The temperature of the perfusate was kept at 37 ± 0 5 C by a water jacketed coil condenser at the inflow Coronary venous outflow was collected in a funnel and returned to the donor jugular vein via the second head of the roller pump The surface of the heart was kept moist by frequent application of 0 9 per cent NaCl solution warmed to 37 C

Four sets of bipolar silver recording electrodes were sewn to the atrial epicardial surface One set was placed on the anterior left atrium over Bachman s bundle approximately 35 mm from the stimulating electrodes (see below) One set was placed either on the left atrial appendage or on the posterior surface of the left atrium beneath the pulmonary veins about 65 mm from the stimulating electrodes in either case Electrodes were sewn over the sulcus terminalis (20 mm) and either on the tip of the right atrial appendage (30 mm) or on the anterior right atrium less than 10 mm from the stimulating electrodes Potentials from these four electrodes were monitored and recorded with an Electronics for Medicine recorder at 20 cm per second paper speed with filter settings 4/500 Records were analyzed with the aid of a cali

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Reprint req ests to Dr P E. Dresel Department of Pharmacology and Therapeutics, Faculty of Med ne Univers ty f M toba, W n n peg R3E OW3, M n toba, Canada.

We believe that a high amplitude left parasternal lift is produced by two mechanisms (1) excessive right ventricular filling—volume overload—as is most commonly seen in severe tricuspid incompetence, ASD or VSD, this is a late diastolic thrust and is followed by systolic retraction and (2) the left atrial lift when the whole heart is thrust forward by the expanding left atrium This is a systolic thrust

Summary and conclusions

The left parasternal lift has been examined in 20 patients with right ventricular hypertrophy (RVH) without tricuspid incompetence (TI), in 13 patients with pure RVH with severe TI, and in 12 patients with residual pure TI following mitral valve replacement The clinical and kinetocardiographic findings have been compared with those of five cases of ASD and with the left atrial lift of mitral incompetence Right ventricular pressure overload of whatever kind produces a slight, sometimes impalpable and usually invisible systolic lift of long duration High amplitude diastolic lifts of short duration which are readily visible are caused by right ventricular volume overload from severe TI or ASD and have their peak at the first heart sound High amplitude systolic lifts with a peak at the second sound are usually due to mitral incompetence The left parasternal lift has considerable bedside value in diagnosis and is not always due to simple right ventricular hypertrophy

We thank Dr N M Dawber the Superintendent of We worth Hospital for facilities and Miss K Purdon and Mr R Taylor for technical assistance

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From the Department of Pharmacology and Therapeutics Faculty of Medicine University of Manitoba, Winnipeg

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Reprint requests to Dr P E. Dresel Department of Pharmacology and Therapeutics Faculty of Medicine University of Manitoba Winnipeg R3E OW3 Manitoba, Canada.

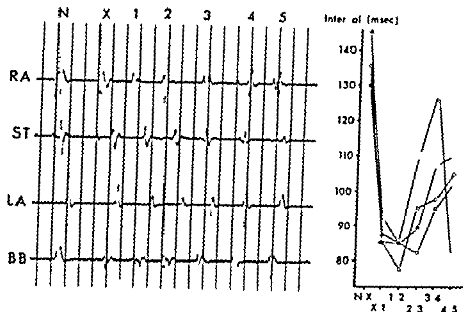


Fig 1 Left side atrial electrograms showing arrhythmia after a single extra stimulus The last beat of the normal drive (N) and the extra stimulus (X) 126 msec later are followed by five unstimulated beats labeled one to five Time lines are 40 msec apart, electrode positions are RA right atrium near stimulus origin ST sulcus terminalis LA left atrium and BB Bachman s bundle Right side order of activation of the electrodes The intervals between successive potentials is plotted for each of the electrode positions Intervals between the last normal beat the single extra stimulus and each unstimulated beat are shown Symbols O RA □ LA △ ST ○ BB

brated loupe with conduction times measured with a precision of ± 0 5 msec from the stimulus artifacts to where the intrinsic biphasic deflection of the atrial electrograms crossed the baseline

The hearts were driven at rates sufficient to suppress natural pacemakers with steel clip electrodes placed on or near the sinoatrial (SA) node A Tektronix stimulator (Type 161 162) yielded 5 msec square wave pulses of 1 5 threshold strength The basal drive was electronically counted and one to four extra stimuli were added after every twentieth beat These were timed by a quartz crystal controlled pulse generator (Digitimer Devices) The regular drive could be interrupted for variable periods during and after the extra stimuli

Acetylcholine chloride (Sigma Chemicals) was infused into the perfusate by means of a continuously variable Harvard pump, and its concentration calculated by measuring the venous outflow

Results

The effects of single extra stimuli Extra stimuli placed early in diastole resulted in speeding of conduction of up to 15 per cent to all electrode positions This phase of supernormal conduction was present in 9 out of 14 hearts and occurred most commonly at coupling intervals of 140 to 200 msec [11,12] By placing an extra stimulus progressively earlier i e, beyond the supernormal period it was possible to produce a transient arrhythmia consisting of 1 to 10 unstimulated beats starting less than 150 msec after the last stimulus Fig 1 shows a typical occurrence The top tracing taken from an electrode 6 mm from the stimulus electrode shows large stimulus artifacts which precede the atrial electrograms of the last beat of the regular drive (N) and of the single extra stimulated beat (X) Starting 90 msec after the last stimulus there is a series of five unstimulated beats at an irregular rate of approximately 600 per minute The shape of the potentials differs between the stimulated and unstimulated beats this is especially noticeable in the top tracing The right half of Fig 1 compares the order of activation of the electrodes by plotting the intervals between successive potentials If the origin of the unstimulated beats were tissue under the stimulating electrode the intervals between successive potentials would most probably be similar for all of the electrodes This was not the case, especially for the last three unstimulated beats all of which appear to have originated from different loci

Effects of multiple extra stimuli Arrhythmia could only infrequently be produced with a single

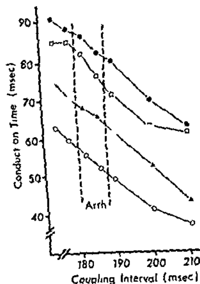


Fig 2 Conduction times to the four electrodes of a second extra stimulus as the coupling interval is decreased. Times are plotted from the last normal beat The first ineffective extra stimulus was given at 90 msec Arrhythmia occurred at the times shown between the dotted lines Symbols as in Fig 1

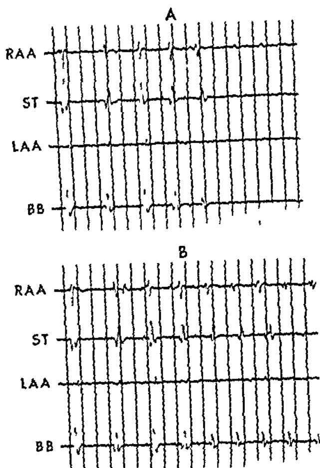


Fig 3 Sequences of extra stimuli that are ineffective and effective in producing arrhythmia Explanation in test Electrode positions RAA right atrial appendage ST sulcus terminalis LAA left atrial appendage and BB Bachman's bundle

extra stimulus We therefore introduced series of up to four extra stimuli in most experiments The first of the series was timed 5 to 10 msec after the effective refractory period (ERP)[15] and a second stimulus was added at progressively shorter intervals until arrhythmia was produced or the ERP was reached Third and fourth extra stimuli were also added, with the preceding stimuli placed 5 to 10 msec outside the ERP or at intervals 5 to 10 msec. longer than the maximum interval at which they had caused arrhythmia Two stimuli were sufficient to cause arrhythmia in most hearts Series of three or four stimuli were always effective Nevertheless our data do not indicate a statistically significant difference between two three and four stimuli in their efficacy to produce arrhythmias However repeated production of transient arrhythmias by multiple extra stimuli facilitated the production of arrhythmias by stimuli found inadequate previously Thus a single previously ineffective stimulus was often able to produce arrhythmias for a short time following repeated arrhythmias produced by multiple extra stimuli

Fig 2 shows the conduction times of a second extra stimulus as the coupling interval was shortened in steps of 4 msec Arrhythmia occurred when this stimulus was timed 182 and 186 msec. after the last normal driven beat (92 and 96 msec after the first extra stimulus of the series) but the very earliest conducted beats did not produce arrhythmia Thus, there is a limited range of coupling intervals over which arrhythmia could be produced. A similar range could be demonstrated one or more times in six out of seven hearts by some combination of one or more stimuli but in many other cases the range of effective coupling intervals reached the effective refractory period. The width of the range within which arrhythmia could be induced varied from 4 to 24 msec

We found no indication of altered conduction to the various recording sites of stimuli which caused arrhythmia The curves of conduction times in Fig 2 are parallel within the arrhythmic range This was the general finding The single exception was an experiment in which there was rapid change in conduction times to

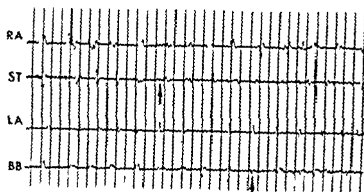


Fig 4 Onset of fibrilatory arrhythmia Explanation in text. Electrode positions as in Fig 1

the sulcus terminalis electrode, producing a sigmoid shaped curve within the arrhythmic range

Fig 2 shows that extra stimuli which cause arrhythmia appear to have the same conduction times as extra stimuli which do not, except for the small changes due to increasing refractoriness This is illustrated in Fig 3 Fig 3, *A* shows atrial electrograms from a heart in which the last beat of the regular drive as well as four extra stimulated beats are seen In Fig 3 *B* the last stimulated beat is timed only 2 msec earlier than in Fig 3 *A* Multiple unstimulated beats now follow There is no difference in the shape of the stimulated potentials between *A* and *B* and the conduction times of the last stimulated beat in *B* are only 1 to 3 msec longer than in *A* This was true in all the hearts studied Thus the production of arrhythmia could never be associated with specific changes in conduction to any of the electrodes

Effects of acetylcholine Acetylcholine chloride was infused at varying rates to obtain concentrations of 0 5 to 8 0 μg per milliliter As expected there was speeding of conduction of normal driven beats and of extra stimuli The effective refractory period was diminished and the supernormal phase of conduction abolished [11,12] Acetylcholine facilitated the production of atrial arrhythmias Concentrations below 2 5 μg per milliliter usually had no effect High concentration (4 to 8 μg per milliliter) caused a sustained atrial arrhythmia with onset during the regular drive We define sustained arrhythmia as one which persisted until shortly after cessation of the infusion With intermediate concentrations of acetylcholine transient or sustained and often disorganized atrial arrhythmias could be produced by extra stimuli Multiple extra stimuli and shorter coupling intervals favored the production of a sustained arrhythmia but the acetylcholine concentration was also critical in determining the type of arrhythmia

A single extra stimulus could produce transient arrhythmia in all hearts in the presence of intermediate concentrations of acetylcholine Arrhythmias produced by extra stimuli were studied in the same manner as described above for the control conditions. Changes in conduction times to any of the electrodes again could not be related causally to the production of arrhythmias

Onset of disorganized arrhythmias This arrhythmia was characterized by continuous, rapid, low voltage activity recorded from at least one electrode There were two modes of onset. Fig 4 shows an experiment in which the onset of disorganized activity was abrupt The last beat of the regular drive and one extra stimulus timed 116 msec later are followed by a sustained arrhythmia The top two tracings taken from the right atrium show the arrhythmia beginning with three well formed potentials more than 80 msec apart The top tracing was taken from a site less than 10 mm from the stimulating electrode The second tracing, taken from the sulcus terminalis shows the abrupt onset of disorganized activity at the arrow Before the onset of disorganized activity the electrode on the sulcus terminalis was activated later than the anterior right atrium except for the beat immediately preceding the arrow in which the activations occur simultaneously The left atrial electrode stopped following the other recording sites at the same time, but disorganized activity did not result from this change in order of activation The electrode near Bachman's bundle first shows an irregular series of unstimulated beats timed 80 to 100 msec apart Four hundred milliseconds after disorganized activity appeared in the sulcus terminalis electrode, similar activity appears in this record at the arrow Note that the rate of the unstimulated beats did not accelerate prior to the abrupt onset of disorganized activity This illustration is typical in that disorganized activity was often recorded by one or two electrodes without involvement of the other sites The site from which disorganized activity was first recorded varied. The other mode of onset is shown in Fig 5 Here, disorganized activity begins after an accelerating tachycardia

The last normal beat and three stimulated extra beats are followed by unstimulated beats at a rapidly increasing frequency leading shortly to disorganized activity under the Bachman s bundle electrode This process is also seen in the other left atrial electrode but is not reflected in electrograms taken from the right atrium The two modes of onset of disorganized activity were seen with equal frequency each heart usually showing only one kind The dissociation of frequency of activation between atria and between electrodes on the same atrium demonstrated in Figs. 4 and 5 was seen commonly

Variability in the conduction times produced by acetylcholine Acetylcholine caused dose related variations in the conduction times of extra stimuli This was studied by recording consecutive sequences of a single extra stimulus introduced at a constant coupling interval after every twentieth beat of the regular drive Fig 6 *A* shows the results in the absence of acetylcholine there is little variability in the conduction times of the extra stimulus In Fig 6 *B* acetylcholine was present at a concentration of 2 6 μg per milliliter an amount insufficient to allow the production of arrhythmia in that heart Considerable variability is demonstrated in the conduction times to the electrodes although none of these beats were followed by an arrhythmia of any kind. In Fig 6 *C* acetylcholine was present at 3 1 μg per milliliter an amount sufficient to allow the induction of sustained disorganized arrhythmias when multiple extra stimuli were introduced. At this concentration there is gross variability and transient arrhythmias occurred after several of the (single) extra stimuli The shape of the potentials also varied. The other two electrodes showed the same variations in conduction times illustrated in Fig 6 *C* However many examples were seen in which variations of conduction times between the same beats were widely different between electrode positions Whenever great variability was seen a sustained disorganized arrhythmia could be induced quite easily by additional extrasystoles by changes in the timing of the single extrasystole or without known change in experimental conditions (Fig 7) Despite the gross variability specific changes in conduction to any one electrode or in the pattern of conduction to the four electrodes could not be linked to the subsequent occurrence of arrhythmia either transient or sustained. An extra

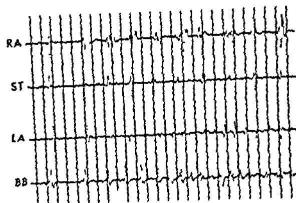


Fig 5 Onset of fibrilatory arrhythmia Explanation in text Electrode positions as in Fig 1

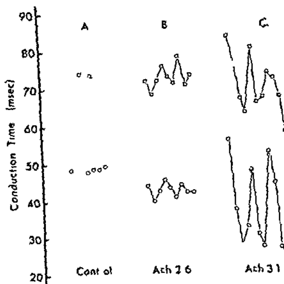


Fig 6 Variability of conduction times caused by acetylcholine Consecutive sequences of conduction times of extra stimuli interpolated after every twentieth normal driven beat without acetylcholine present (control) at 2 6 μg per milliliter and at 3 1 μg per milliliter Symbols as in Fig 1

beat resulting in arrhythmia could be conducted slower faster or the same as the immediately preceding extra beat which did not cause arrhythmia Fig 7 illustrates this point with consecutive sequences showing the last normal beat followed by an extra stimulus 90 msec later In Fig 7 *A* the extra stimulus is not followed by any arrhythmia while in Fig 7 *B* a sustained but not disorganized arrhythmia ensues The conduction times of the stimuli are the same in *A* and *B*, as are the shapes of the stimulated potentials

In two hearts, a disorganized arrhythmia

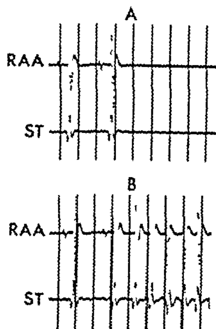


Fig 7 Variability in efficacy of a single extra stimulus *A* coupling interval 90 msec no arrhythmia *B* after 19 beats at the usual rate coupling interval the same arrhythmia

which reverted spontaneously within 30 to 180 seconds could be induced in the absence of acetylcholine Gross variability of conduction times was also found under these conditions Variability was not seen in other hearts under similar conditions when a prolonged arrhythmia could not be induced

Discussion

Extra stimuli placed early in the diastolic period produced transient arrhythmias Our hypothesis was that the effectiveness of such extra stimuli should be associated with a change in the pattern of their conduction to the recording electrodes However we failed to demonstrate any changes in conduction that could be related causally to the production of arrhythmia either in the presence or the absence of acetylcholine

Explanations for the mechanism allowing production of arrhythmia must consider the major theories concerning atrial arrhythmia i e a circus movement activation of latent automatic foci, and re entry The possibility of a classic circus movement of Rosenblueth and Garcia Ramos[16] is unlikely because there was no regularity in the sequence in which the electrodes were activated during arrhythmia (Fig 1) because we show that the activity could be local (Fig 4), and because the unstimulated beats came at an irregular frequency Our results are, therefore clearly different from those of Allessie Bonke, and Schopman[17] who demonstrated recently that tachycardias induced by single extrasystoles in isolated rabbit left atria are due to circus movements Differences in the size of the atria, the species or the oxygen supply as well as the possible exclusion of the atrial conducting system from their preparations may all have contributed to the opposite results in the two laboratories Activation of a single rapidly firing focus as proposed by Scherf[18] is unlikely The arrhythmias appeared to originate from multiple regions of the atria their rate was irregular and was different at different recording sites

The sinus node has been shown to be of importance in the production of atrial fibrillation[19] Multiple re entry at this location cannot be excluded in some of our experiments (Figs 5 and 7) but other experiments show that this cannot be the only site of origin of the unstimulated beats

Supra threshold induction shocks in the ventricle[20] as well as 1 5 × threshold shocks in the atria[5] have been shown to cause high frequency discharges from under the stimulating electrode Electrograms in those studies showed an accelerating series of potentials best seen near the stimulating electrode We cannot exclude this mechanism in some of our experiments in which an accelerating tachycardia was observed in some electrodes However other experiments represented by Fig 4 are incompatible with this mechanism because even electrodes very close to the stimulus origin do not show an accelerating tachycardia

A re entry mechanism in the body of the atria best fits our observations The multiple sites of origin of the unstimulated beats might be expected with re entry occurring at different sites within the tissue The existence of a range of coupling intervals within which arrhythmia could be induced is also suggestive since the timing of extrasystoles is critical for the occurrence of re entry Stimuli timed too early or too late would fail to complete the re entry pathway Acetylcholine which facilitated the production of and changed the character of the arrhythmias is well known to shorten the refractory period and to speed conduction We have shown that acetylcholine produces variability in conduction times to the sites of the recording electrodes variability that is not always in the same direction for different electrode positions We also observed that the shape of the potentials

produced by early extra stimuli were variable after acetylcholine suggesting that multiple pathways for activation of the recording sites were present after the drug All these properties would enhance the possibility for re entry We observed that one electrode or one atrium frequently showed disorganized activity while the other electrodes showed activity at a much slower frequency (Fig 5) This indicates conduction block a necessary condition for re entry Unidirectional block and greatly abbreviated action potentials have recently been demonstrated to occur in atrial tissues under special conditions[21] These phenomena have been shown by Sasyniuk and Mendez[22] to be important precursors for re entry occurring in the ventricle Sharma[23] showed evidence for re entry in aconitine induced arrhythmias but did not observe dissociation of the atria However Byrne and Dresel[24] have observed inter atrial block during the recurrence of aconitine induced atrial fibrillation after direct current counter shock

Re entry in the ventricle has been demonstrated at junctions with a low safety factor of conduction as well as at sites where conduction velocities differed in adjacent groups of cells [2 25] The atrial musculature has generally been considered to be syncytial but considerable attention has been given recently to specialized conducting fibers which differ from muscle in having a faster conduction velocity and a longer refractory period. Acetylcholine shortens refractoriness more in muscle than in conducting fibers thus increasing the differential between them [11] It would appear possible therefore that junctions of atrial muscle and conducting system fibers may be involved in atrial re entry

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Effects of hemodialysis-induced hypokalemia and hypomagnesemia on blood pressure in dogs

Walter J Hoppe, M S *
Thomas E Emerson, Jr , Ph D
East Lansing Mich.

It is well known that electrolyte abnormalities occur in certain hypertensive disorders It is also established that small decreases in plasma potassium or magnesium concentrations or osmolarity alone or in combination are vasoconstrictors in most vascular beds [1] Because of this phenomenon, two studies were initiated recently to determine whether small acute electrolyte abnormalities could increase blood pressure in intact dogs In one study hypokalemia and hypomagnesemia were produced acutely by hemodilution in the presence of hypervolemia [2] while in the second study [3] the same abnormalities were produced by a technique involving a potent diuretic (furosemide) In both of these studies a moderate increase in systolic diastolic and mean blood pressure was demonstrated However in both studies factors were present in addition to the electrolyte abnormalities which make interpretation of these data difficult For example it is possible the hypervolemia in the former study or the diuretic in the latter might have influenced or altered the response which might have occurred in the absence of these predisposing conditions Also complicating the picture are studies in which similar but chronically induced electrolyte abnormalities created by dietary depletion demonstrated a fall in blood pressure rather than an increase [4-6]

The current study was undertaken to test the hypothesis that moderate hypokalemia or the combination of hypokalemia and hypomagnesemia causes an increase in systemic arterial blood pressure in the dog These electrolyte abnormalities were created using a clinical dialyzer and conditions were such that other plasma electrolytes and body fluids were unaltered.

Methods

Sixty four mongrel dogs of both sexes anesthetized with sodium pentobarbital (30 mg per kilogram) and anticoagulated with heparin (5 mg per kilogram) were used for this study Average dog weight was 16 kilograms (range 10 to 20 kilograms) The dogs were ventilated with a Harvard respirator via an endotrachial tube

Both femoral arteries and veins were cannulated and the catheters (PE 320 tubing) advanced into the abdominal aorta and inferior vena cava respectively The left femoral arterial catheter was used for monitoring arterial blood pressures and heart rate and for obtaining blood samples The left femoral vein catheter, placed near the right atrium was used for measuring central venous pressure Blood pressures were recorded using Statham pressure transducers and a Sanborn direct writing recorder

Plasma electrolyte changes were produced by dialysis utilizing the extracorporeal set up shown in Fig 1 A roller type blood pump (Holter) was interposed between the right femoral arterial catheter and the hemodialyzer (Western Kiil 7200) Blood outflow from the dialyzer was directed to the left femoral vein Flow was held constant at 150 ml per minute The dialyzer was primed with crossmatched whole blood (240 ml)

From the Department of Physiology Michigan State University East Lansing

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Reprint requests to Dr Thomas E Emerson Jr Department of Physiology Giltner Hall Michigan State University East Lansing Mich 48824

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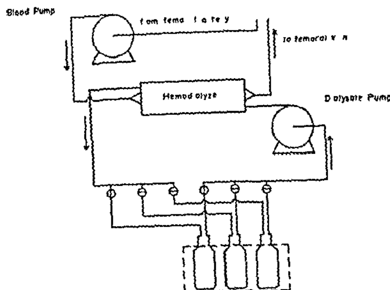


Fig 1 Schematic diagram shows the blood circuit and dialysate circuit The temperature of the dialysate solu tion is maintained at 37 C in a constant temperature water bath.

Table I Experimental protocol

Condition	G oup	N	Control 0 30 min.	Experimental 30 60 min.	Postexperimental 60 90 min.
Control	1	9	Normal	Normal	Normal
↓K	2	10	Normal	No K^+	Excess K^+
↓K ↓Mg	3	10	Normal	No K or Mg +	Excess K^+ and Mg^{++}
Spinal block control	4	9	Normal	Normal	Normal
Spinal block ↓K	5	10	Normal	No K	Excess K^+
Spinal block ↓K ↓Mg	6	10	Normal	No K or Mg^+	Excess K^+ and Mg^{++}

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from a donor dog Plasma fluid which was filtered from the blood passing through the dialyzer was replaced by intravenous infusion as it was formed.

The experimental protocol used in all the groups consisted of three sequential 30 minute periods of dialysis during which the animal s ar terial blood was dialyzed against three separate dialysate solutions contained in a water bath kept at 37 C The dialysate solutions were changed from one to the other with uninter rupted flow by means of a valving arrangement Ten milliliter blood samples were taken for elec trolyte measurements at the end of the first 30 minute period (control sample) and every 15 minutes thereafter Each sample was replaced by 10 ml of dextran given intravenously Plasma electrolyte concentrations were determined in duplicate as follows K^+ and Na by flame pho tometry (Beckman Model 105) and Mg + and Ca by atomic absorption (Perkin Elmer atomic absorption spectrophotometer Model 290B) Blood hematocrit and plasma osmolarity were determined with a microhematocrit centrifuge and advanced osmometer (freezing point depres sion) respectively Arterial blood pH was meas ured with a pH meter (22 Astrup Radiometer)

The experimental protocol is depicted in Table 1 The solutions used were normal Ringer s solu tion (concentration in milliequivalents per liter Na 146 Mg 2 K^+ 4 Ca^{++} 5 Cl 131 HCO_3^- 21 measured osmolality 300 mOsm per liter) or

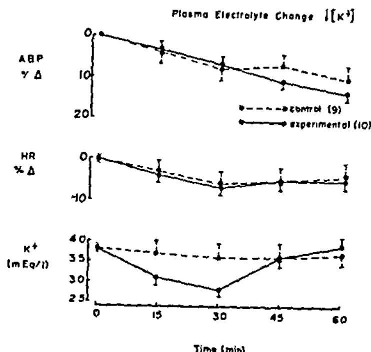


Fig 2 Summary of mean arterial blood pressure (ABP) and heart rate (HR) responses during hypokalemia Responses are expressed as a per cent change (% Δ) relative to 0 minutes over the 60 minute dialysis interval

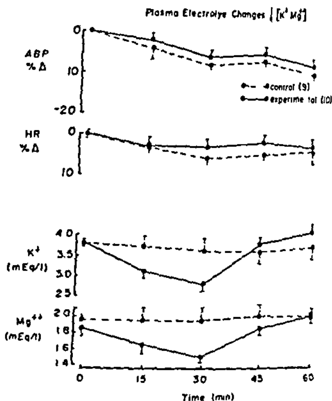


Fig 3 Summary of mean arterial blood pressure (ABP) and heart rate (HR) responses during hypokalemia and hypomagnesemia. Responses are expressed as a per cent change (% Δ) relative to 0 minutes over the 60 minute dialysis interval

modified Ringer's solution lacking or containing an excess of the test ion(s) Dialysate concentration of the latter solutions were 7 mEq per liter (K^+) and 3 5 mEq per liter (Mg^{++}) which were sufficient to return the plasma concentration of these cations to near pre experimental levels Osmolarity of each experimental solution was adjusted to normal by altering the Na^+

Involvement of the neurologic barostatic system in the observed responses was evaluated in dogs whose barostatic mechanism was rendered inoperable by spinal anesthesia (Table I Groups 4 through 6) An average of 7 ml of cerebrospinal fluid was withdrawn from the cisterna magna and replaced with an equal amount of 2 per cent procaine hydrochloride solution (Abbott), infused slowly over a 4 to 5 minute period, supplemental doses were given as needed Effectiveness of the spinal block was tested by eliciting the carotid sinus reflex (bilateral common carotid artery occlusion) before and after spinal anesthesia no response after procaine administration indicated an effective block This test was performed periodically throughout the experiment At the end of the experiment the spinal block was further checked by allowing the dog to breathe voluntarily Failure of spontaneous respiration at the end of the experiment was further evidence of an effective spinal block

Statistical analysis of the data was performed using Student's t test modified for paired replicates for within group comparison and the standard Student's t test for comparison of means between groups

Results

Figs 2 through 5 depict changes in arterial blood pressure and heart rate expressed as per cent change from control Also shown are the electrolyte changes created by the dialysis procedure Actual values appear in Table II, along with other hemodynamic data and information on other plasma electrolyte concentrations and osmolarity

It is reasonably clear from these experiments that in the intact dog decreasing plasma [K^+] singly (Fig 2) or in combination with hypomagnesemia (Fig 3) does not produce changes in systemic blood pressure or heart rate significantly different than those occurring in control experiments in which dialysis procedure was identical but the plasma electrolyte concentrations were unaltered

Fig 4 shows that hypokalemia produced in dogs with their neurologic barostatic mecha

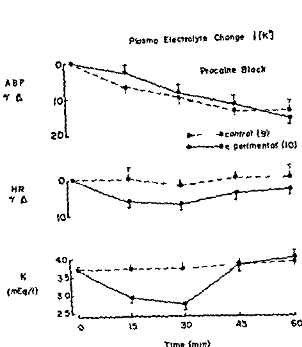


Fig 4 Summary of mean arterial blood pressure (ABP) and heart rate (HR) responses during hypokalemia in spinally anesthetized animals Responses are expressed as a per cent change (% Δ) relative to 0 minutes over the 60 minute dialysis interval

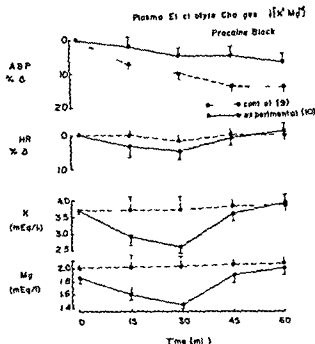


Fig 5 Summary of mean arterial blood pressure (ABP) and heart rate (HR) responses during hypokalemia and hypomagnesemia in spinally anesthetized animals Responses are expressed as a per cent change (% Δ) relative to 0 minutes over the 60 minute dialysis interval

nisms rendered inoperable also does not result in hemodynamic changes different than those occurring in control animals However data shown in Fig 5 which was obtained from dogs with spinal blockade suggest that the combination of hypokalemia and hypomagnesemia causes an increase in mean arterial blood pressure While blood pressure in the experimental group did fall slightly the decrease was only half as great as seen in control dogs ($P < 0.05$) This difference between experimental and control animals is perhaps related to changes in cardiac output and/or total peripheral resistance occurring in the experimental dogs as a result of the electrolyte abnormalities Heart rate changes in both groups were similar

Discussion

Results obtained from this study were indeed unexpected As mentioned previously hypokalemia or the combination of hypokalemia and hypomagnesemia are associated with increases in systolic diastolic and mean blood pressures when the abnormalities are induced by hemodilution[2] or by diuresis[3] Additionally the increment in blood pressure is enhanced by spinal blockade[7] Also our data are surprising when one considers the known effects of these plasma electrolyte abnormalities on the two direct determinants of arterial blood pressure cardiac output and total peripheral resistance Both hyperkalemia[8,12] and hypermagnesemia[13] have been shown to decrease myocardial contractility Recent evidence suggests that both acute hypokalemia[3,10,14,15] and chronic dietary hypokalemia[4] produce an increase in myocardial contractile force The effects of these ionic abnormalities on total peripheral resistance are not as well defined However in a recent study we showed that the opposite abnormalities produced by infusing small amounts of isotonic electrolyte solutions intravenously resulted in a fall in total peripheral resistance in spinally blocked dogs[16] and the effects of these abnormalities on resistance in many peripheral vascular beds is well established[17,18] An acute local decrease in the plasma [K] causes arteriolar constriction in the forelimb[8] renal[8] and skeletal muscle[19,20] vascular beds of the dog Also pertinent to the present study is the enhanced vasoconstriction seen when hypokalemia is created in combination with hypomagnesemia in the perfused dog

Table II Average effects of control and experimental hemodialysis on blood pressures heart rate, and measu

Group No	Event	N	Mean blood pressure (mm. Hg)					Systolic blood pressure (mm. Hg)					Diastolic blood pressure (mm. Hg)					Heart rate (beats/min.)					Hematocrit (%)				
			0	15	30	45	60	0	15	30	45	60	0	15	30	45	60	0	15	30	45	60	0	15	30	45	[illegible]
1	Control	9	111	107	104	103	100	127	124	120	120	118	98	94	90	91	87	143	139	134	135	136	39	40	40	40	[illegible]
2	Hypokalemia	10	109	105	102	97	94	129	129	123	119	114	95	93	88	84	79	146	139	136	138	139	41	41	42	[illegible]	[illegible]
3	Hypokalemia, hypomagnesemia	10	110	108	103	104	100	129	130	121	122	119	97	93	89	90	86	143	138	138	140	138	39	40	[illegible]	43	[illegible]
4	Control	9	70	65	62	59	69	87	82	78	76	78	58	53	51	47	48	108	108	106	108	108	36	37	37	37	[illegible]
5	Hypokalemia	10	69	67	64	61	59	87	85	81	77	76	58	56	54	50	48	105	98	98	101	101	40	40	40	40	[illegible]
6	Hypokalemia hypomagnesmia	10	68	66	64	65	64	83	81	80	83	82	56	53	52	54	52	113	109	107	111	113	39	40	41	41	[illegible]

Zero 15 30 45 and 60 signifies duration of experiment in minutes. Groups 1 through 3 represent an unblocked animal series Groups 4 through 6 represe
* = $P < 0.05$ relative to the above control

forelimb or kidney[18] or gracilis muscle[21] It is equally well established that acutely produced local hyperkalemia causes active dilation of pre capillary vessels in all vascular beds studied[22-30] excepting the portal venous system[31] At first ap pearance results of the present study are not compatible with the studies involving techniques mentioned previously in which electrolyte abnor malities were produced acutely[2,3] or with the studies involving chronic potassium depletion[4,5] In the former studies, blood pressure increased consistently while in the latter it decreased Data from the current study also are not com patible with the hypothesis that small multiple electrolyte disorders are solely responsible for chronic blood pressure elevation seen in certain forms of hypertension which are also associated with various single or multiple electrolyte abnor malities An explanation for these differences is at best, difficult However perhaps the time fac tor and/or experimental conditions in the dilu tional studies are involved whereas in the diuretic study modification of the response by the diuretic cannot be ruled out In the chronic dietary studies other factors are most probably involved in the eventual blood pressure change

Finally, our study suggests that the combina tion of hypokalemia and hypomagnesemia causes an increase in arterial blood pressure which is effectively buffered by the neurologic barostatic system While our study does not sup port the hypothesis tested it does not rule out the likelihood that plasma electrolyte abnormalities act in unison with other abnormalities to produce chronic essential hypertension

Summary

Experiments were completed in dogs to test the hypothesis that mild hypokalemia or the com bination of hypokalemia and hypomagnesemia cause an increase in systemic arterial blood pressure Results indicate that under the condi tions of this study, mild hypokalemia or the com bination of hypokalemia and hypomagnesemia does not produce changes in blood pressure different than those observed in control dogs in which blood pressure consistently fell Addi tionally, hypokalemia alone did not affect systemic blood pressure in dogs with their neurologic barostatic system rendered inopera ble The significant finding of the study is that the blood pressure fall was not as marked in dogs with a spinal block in which hypomagnesemia and hypokalemia were created simultaneously

od parameters

pH (units)					*K⁺ (mEq/L)*					*Mg⁺⁺ (mEq/L)*					*Ca⁺⁺ (mEq/L)*					*Na⁺ (mEq/L)*					*Osmolarity (mOsm/L)*				
0	15	30	45	60	0	15	30	45	60	0	15	30	45	60	0	15	30	45	60	0	15	30	45	60	0	15	30	45	60
37	7 36	7 35	7 35	7 35	3 8	3 7	3 6	3 6	3 7	1 96	1 96	1 97	2 00	2 00	4.5	4 5	4 5	4 5	4 5	150	150	151	150	151	299	298	299	299	299
28	7 31	7 29	7.30	7.30	3 8	3 1	2 8	3 6	3 9	2 00	2 00	2 00	2 13	2 11	4 7	4 6	4 6	4 6	4 7	149	151	150	151	151	297	298	299	300	300
28	7 25	7 24	7 22	7.23	3 8	3 1	2 8	3 8	4 1	1 94	1 64	1 49	1 87	2 01	4 6	4 6	4 5	4 5	4.5	148	148	149	149	149	299	299	300	300	301
38	7 39	7 37	7 38	7 36	3 7	3 7	3 7	3 8	3 9	2.02	2 04	2 04	2 05	2 08	4 7	4 6	4 6	4 6	4 6	150	150	150	150	151	298	299	299	299	300
.36	7 35	7 33	7 34	7 34	3 7	2 9	2 8	3 8	4 0	1 92	1 94	1 95	1 95	1 94	4 5	4 6	4 6	4 6	4 6	150	152	153	152	152	299	299	299	300	301
7 34	7.32	7 3?	7 31	7 32	3 7	2 9	2 6	3 6	3 9	1 86	1 60	1 46*	1 89	2 01	4 6	4 6	4 5	4 6	4 5	147	147	148	148	149	291	292	291	292	292

spinally blocked series

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5	Hypokalemia	10	69	67	64	61	59	87	85	81	77	76	58	56	54	50	48	105	98	98	101	101	40	40	40	40	40
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Finally, our study suggests that the combina tion of hypokalemia and hypomagnesemia causes an increase in arterial blood pressure which is effectively buffered by the neurologic barostatic system While our study does not sup port the hypothesis tested it does not rule out the likelihood that plasma electrolyte abnormalities act in unison with other abnormalities to produce chronic essential hypertension

Summary

Experiments were completed in dogs to test the hypothesis that mild hypokalemia or the com bination of hypokalemia and hypomagnesemia cause an increase in systemic arterial blood pressure Results indicate that under the condi tions of this study mild hypokalemia or the com bination of hypokalemia and hypomagnesemia does not produce changes in blood pressure different than those observed in control dogs in which blood pressure consistently fell Addi tionally, hypokalemia alone did not affect systemic blood pressure in dogs with their neurologic barostatic system rendered inopera ble The significant finding of the study is that the blood pressure fall was not as marked in dogs with a spinal block in which hypomagnesemia and hypokalemia were created simultaneously

Direct arterial pressure, pulse rate, and electrocardiogram during micturition and defecation in unrestricted man

W A Littler MD MRCP
A J Honour MA DPhil
P Sleight MD FRCP
Oxford, England

Micturition and defecation may be associated with dramatic cardiovascular events such as syncope and collapse due to pulmonary embolism Little is known about the changes in arterial pressure or heart rate which accompany normal excretory events

In paraplegic patients increased arterial pressure sweating and skin vasoconstriction have been shown to accompany bladder filling and rises in intravesical pressure [1-3] The decrease in skin blood flow was attributed to active vasoconstriction as a result of a spinal reflex Corbett and colleagues[4] further demonstrated that bladder percussion produced contraction of the wall of the bladder and this was associated with increased arterial pressure decreased heart rate and calf and hand blood flow These responses occurred whether there was a rise in intravesical pressure or not

It was therefore of interest to study the circulatory changes associated with normal excretory events during measurement of blood pressure and electrocardiogram over 24 hours in ambulent subjects outside hospital.

Patients and methods

Eleven patients who had accurately indicated the time of micturition and defecation were chosen from a larger group in whom direct arterial pressure heart rate and electrocardiogram have been recorded continuously over a 24 hour period Their details are listed in Table I All patients gave informed consent to the study in which the methods used have been previously described[5] The patients were studied over a 24 hour period from 9 00 A.M to 9 00 A.M During this time they attended the laboratory only once for 15 minutes after a 12 hour interval, to calibrate and service the apparatus Significant events were recorded simultaneously on the tape and in a diary kept by the patient

After preliminary inspection of our results, each selected event was played out so that a visual beat to beat analysis could be achieved. The records were also scrutinized for changes in cardiac rhythm and ST segment shift[6]

Results

A total of 35 episodes were clearly indicated by 11 patients these consisted of 25 episodes of micturition and 10 episodes of defecation (one in each patient apart from Case 4)

The characteristic pattern of cardiovascular response observed, irrespective of whether the subject micturated or defecated, was essentially a Valsalva maneuver[7] (Tables II and III) Fig 1 is a typical example from a 27 year old schoolteacher who developed systemic hypertension while taking oral contraceptives With the onset of micturition there was a brief rise in arterial pressure followed by a precipitous fall to a level of 108/82 mm Hg when it rose to an alarming 282/169 mm Hg with the overshoot Reflex bradycardia occurred during the overshoot period widening the RR interval from 0 69 second at the beginning to 1 0 second. This Valsalva pattern was observed in varying degree during micturition in 21

From the Departments of Cardiovascular Medicine and the Regius Professor of Medicine Radcliffe Infirmary Oxford, England

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Reprint requests to Dr W A Littler Department of Cardiovascular Medicine Radcliffe Infirmary Oxford, England.

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W A Littler, MD MRCP
A J Honour MA DPhil
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From the Departm nts of Cardiovasc lar Med c ne and the Regius Professor of Medi i Rad l ffe Infi mary Oxford, Engl nd.
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Repri t requests to Dr W A. Little Department of Cardiov scul Medicine Radcl ff Infirmary Oxford, England.

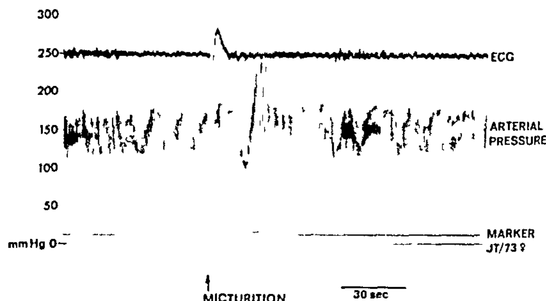


Fig 1 A tracing from a 27 year-old woman who developed hypertension while taking oral contraceptives (Case 3) Note that the predominant changes in arterial pressure are those of a Valsalva response (see text) with reflex slowing of the heart during the overshoot period

Table I Patient data

Patient	*Age (yr)*	*Sex*	*Occupation*	*Diagnosis*	*Treatment*	*Resting BP*
1	50	M	Doctor	Essential hypertension	–	140/100
2	20	M	Factory worker	Normotensive	–	120/70
3	23	F	Teacher	Hypertension (Pill)	–	180/115
4	35	M	Doctor	Normal	–	136/84
5	33	F	Psychologist	Normal	–	110/70
6	22	F	Teacher	Essential hypertension	Propranolol 80 mg daily Aldactide 400 mg	150/110
7	39	F	Housewife	Renal hypertension	Bethanidine 20 mg tds	180/115
8	54	M	Engineer	Angina	Propranolol 80 mg tds Glyceryl trinitrate	125/75
9	55	M	Factory worker	Pheochromocytoma	–	220/130
10	20	M	Student	Normal	–	138/82
11	62	F	Housewife	Essential hypertension angina	Methyl dopa 750 mg Practolol 300 mg Glyceryl trinitrate Digoxin 0 25 mg	200/85

out of the 25 events (86 per cent) It did not occur in Case 7 a woman with renal hypertension receiving bethanidine or Case 11 a 62 year old woman with hypertension and angina receiving methyldopa and practolol In these two patients there was little initial fall in arterial pressure and no overshoot or reflex bradycardia

There were no real quantitative differences between the magnitude of the response in males and females although the largest overshoot +174/82 mm Hg, was in a female (Case 3 Table II) In men, the Valsalva maneuver tended to be repeated several times during micturition with a diminishing response (Fig 2) while the females in general showed one major response (Fig 1) A single Valsalva response extended over 25 to 40 seconds

Fig 3 demonstrates that the arterial pressure after micturition did not show any consistent or significant rise or fall as compared with the level before micturition

During defecation a similar Valsalva response was observed and often repeated several times Fig 4 is a record of defecation in the young

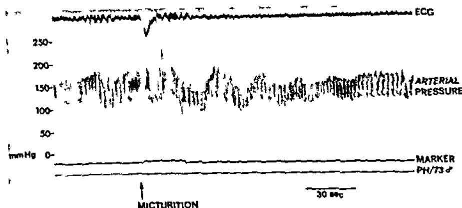


Fig 2 Micturition in a hypertensive man showing at least 3 "troughs and peaks of arterial pressure during the event before the pressure evens out (Case 1)

Table II Micturition (25 events)*

Case	Arterial pressure Control (mm. Hg)	Trough (mm. Hg)	Overshoot (mm. Hg)	R R control (sec.)	R R overshoot (sec)	Duration (sec)
1	180/110	128/86	175/120	0 89	1 14	40
	136/86	114/73	192/86	0 89	1 14	40
2	68/43	36/22	88/63	0 69	0 8	40
	140/83	60/39	170/87	0 69	0 8	30
	137/100	106/87	133/103	0 69	0 8	40
3	133/85	76/51	148/109	0 7	0 9	30
	133/100	123/97	164/121	0 69	0 8	30
4	90/50	67/35	115/65	0 69	1 14	40
	90/50	85/50	104/55	1 09	1 09	30
5	83/59	72/41	103/60	0 62	0 69	30
6	133/85	70/51	148/108	0 69	1 3	30
	133/100	133/97	164/121	0 9	1 4	30
7	123/100	113/100	128/95	0 69	0 69	25
	130/97	127/95	127/95	0 7	0 69	30
8	105/77	80/62	113/88	0 8	1 03	40
	110/80	100/72	120/95	1 03	1 03	31
9	168/104	150/90	202/125	0 60	0 69	40
	164/125	122/82	167/125	0 69	0 80	40
	166/100	140/80	212/110	0 70	1 03	45
10	116/94	109/89	132/97	0 45	0 69	28
	122/97	98/74	129/94	0 [illegible]0	0 83	30
	116/93	91/70	120/93	0 69	1 08	45
	137/83	119/70	137/90	0 69	1 03	40
11	238/117	202/117	190/112	0 69	0 69	40
	212/127	193/120	175/127	0 8	0 80	40

A summary of the most significant cardiovascular changes during each micturition event (see text)

woman whose response to micturition is shown in Fig 1 The responses are clearly similar Fig 5 is taken from a normotensive male patient and shows a Valsalva response towards the end of defecation This pattern was observed in normal hypertensive and angina patients irrespective of their treatment.

Discussion

There are rich reflex interconnections between the bladder and cardiovascular system but little attention has been paid to the behavior of arterial pressure and heart rate in man during micturition with the bladder intact. In mammals the basic cardiovascular response to bladder disten

Table III Defecation (10 events)

Case	Arterial pressure Control (mm. Hg)	Trough (mm. Hg)	Overshoot (mm. Hg)	R R control (sec.)	R R overshoot (sec)	Duration (sec.)
1	142/100	125/90	167/114	0 89	1 14	40
2	150/93	70/39	180/97	0 69	0 8	30
3	130/70	116/59	212/132	0 60	1 03	40
4	–	–	–	–	–	–
5	81/55	59/35	93/61	0 62	0 69	30
6	123/85	90/61	157/102	0 69	1 03	32
7	114/90	95/77	136/100	0 69	0 69	40
8	105/77	80/62	113/88	0 69	0 88	48
9	154/108	118/82	146/110	0 69	0 69	50
10	103/89	85/70	116/96	0 69	1 40	28
11	218/152	175/140	240/165	0 69	1 03	40

A summary of the changes during defecation

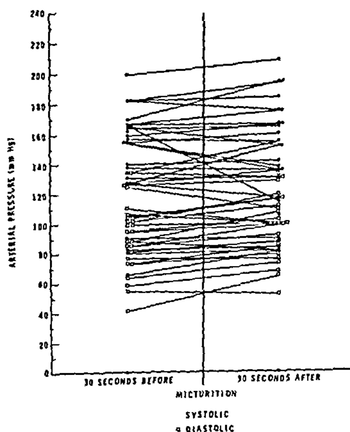


Fig 3 Blood pressure readings averaged over 10 beats 30 seconds before starting and 30 seconds after micturition in both females and males There is no significant alteration in the levels of either systolic or diastolic pressure

tion appears to be vasoconstriction with an accompanying rise in blood pressure These observations have been made mostly under laboratory conditions where the bladder was deliberately distended [1 3]

Muellner[8] believes that the initiation of micturition is not brought about only by impulses to the bladder, but that man develops a voluntary mechanism which is mediated through the use of the intra abdominal pressure and his pelvic floor muscles Furthermore he believes that the direction of intra abdominal pressure towards the vesical neck to initiate the reflexes of voluntary micturition is not normally a straining effort However the respiratory maneuver associated with micturition suggests it may sometimes involve forceful expiration against a closed glottis[7] Proudfit and Forteza[9] believe that a Valsalva maneuver is performed at the beginning and at the termination of micturition our findings, especially in women lend support to this hypothesis

Our patients were allowed complete freedom during the study and the events reported there were clearly marked although we obviously were not able to ascertain how distended their bladders were at that time The most characteristic pattern in the female, illustrated in Fig 1 shows the initial rise, fall and subsequent rise in arterial pressure with an associated reflex bradycardia—i e, a typical Valsalva maneuver Micturition in the female usually takes place in the squatting position which may involve 'strain Alternatively there might be a general vasoconstriction induced through autonomic reflexes by a distended bladder which disappears with bladder emptying and is followed by temporary hypotension However, we have seen neither a big increase or a significant fall in arterial pressure occurring before or after micturition In males especially, the 'peak and trough' effect of the arterial pressure is repeated several times

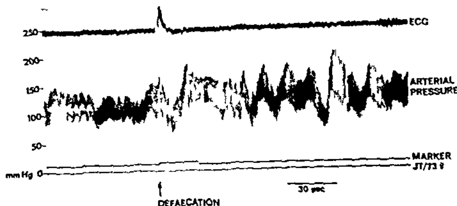


Fig 4 Defecation (Case 3) The arterial pressure trace shows at least four Valsalva responses during this event (compare with Fig 1)

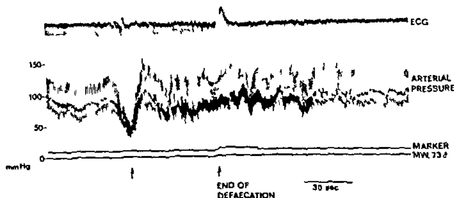


Fig 5 Defecation in a normotensive male (signal indicates end of event in this instance) The most significant change in arterial pressure (*arrows*) is a typical Valsalva response (Case 2)

during micturition suggesting that these may well be associated with straining (Fig 2) Males micturate in a standing position unless associated with defecating and straining movements are often repeated, possibly explaining the cardiovascular changes observed.

Micturition syncope is believed by some investigators to be associated with the circulatory effects of the Valsalva maneuver [9] However this hypothesis is not shared by all [10] Our observations certainly indicate dramatic circulatory changes during micturition but do not show any substantial fall afterwards as occurs with a spinal bladder [3]

It is well recorded that defecation is accompanied by the Valsalva maneuver with the characteristic cardiovascular changes [7] However this work does not state the total number of observations made or the types of patient who were studied. The main cardiovascular feature during defecation in our patients was a Valsalva response often repeated several times during the event (Fig 4)

Patients whether normotensive or hypertensive showed no qualitative differences although responses could have been altered by drug therapy in two patients but numbers were too small to come to any definite conclusion

Our results indicate that very large swings in the level of arterial pressure and heart rate occur during everyday life without the patient being at all aware of them It is surprising in view of some of our figures that subarachnoid and cerebral hemorrhage does not occur more frequently during excretion than at other times

Summary

Eleven unrestricted patients clearly indicated episodes of micturition and defecation during a 24 hour period when their arterial pressure

heart rate and electrocardiogram were recorded continuously

During excretory events in both males and females, the predominant cardiovascular change was a Valsalva maneuver, which in some instances was repeated several times

There was no significant change in the level of arterial pressure following micturition as compared with the level beforehand

These cardiovascular changes were uninfluenced by the presence of essential hypertension or ischemic heart disease, but were modified in some instances by drugs which affected the autonomic nervous system

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Relationship between regional ventricular asynergy and the anatomic lesion in coronary artery disease

B S Lewis M B B Ch
A Bakst, M B , B Ch
M S Gotsman M D F R C P F A C C
Durban, Natal, South Africa

Acute myocardial infarction causes death of muscle in a portion of the ventricular wall. An infarct may be transmural intramural or subendocardial Infarct size and site are related to the site(s) of coronary artery disease the underlying coronary artery anatomy the availability of a collateral circulation and the myocardial oxygen demand it may be modified by therapy Although the effects of acute and chronic myocardial ischemia on cardiovascular dynamics and on left ventricular performance have been studied the relationship of functional abnormalities to defined pathologic lesions of the individual coronary artery has not been determined the presence of multiple lesions complicates analysis[1-7] The availability of high quality angiography to identify areas of regional ventricular dysfunction the understanding that such dysfunction may cause cardiac failure and the potential improvement achieved by excision of the scar have highlighted the importance of ventricular asynergy[8]

This paper will describe the relationship between angiographically determined infarct size and abnormalities of the left ventricular (LV) function in a selected group of patients with specific coronary artery lesions isolated or combined obstruction of the right coronary artery (RCA) and the anterior descending branch of the left coronary artery (LAD) These groups were selected to simplify the analysis and to crystallize the results

Patients

A group of 51 patients was selected for study The patients were divided into three groups

Group I Isolated obstruction of the left anterior descending coronary artery (LAD)[9] Nineteen patients had obstruction of 70 per cent or more of the proximal part of the LAD The obstruction was *incomplete* in seven patients (subset 1A) and complete in 12 patients (subset 1B)

Group II Isolated obstruction of the *right* coronary artery (RCA)[10] Twelve patients had a 70 per cent or greater obstruction of the right coronary artery The obstruction was incomplete in five patients (subset 2A) and complete in seven patients (subset 2B)

***Group III* Combined obstruction of the LAD + RCA**[11] Twenty patients had coronary disease with obstruction of 70 per cent or more of both the RCA + LAD This group was subdivided into four subsets subset 3A four patients had subtotal obstruction of both RCA and LAD subset 3B one patient had complete occlusion of the LAD and subtotal obstruction of the RCA subset 3C six patients had complete occlusion of the RCA and incomplete obstruction of the LAD and subset 3D in nine patients both the RCA and LAD were completely obstructed.

No patient had disease of another coronary artery which produced luminal narrowing of more than 50 per cent.

From the Ca diac Unit, Wentworth Hospital, and the University of Natal, Durb n, South Africa.

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Reprint requests to: Professor M S. Gotsman, Cardiac Unit, Wentworth Hosp tal, P B Jacobs, Natal, South Africa.

Table I Clinical data

	Group 1		Group 2		Group 3			
	Isolated LAD disease		*Isolated RCA disease*		*Disease of LAD + RCA*			
	Subset A subtotal occlusion	*Subset B total occlusion*	*Subset A subtotal occlusion*	*Subset B total occlusion*	*Subset A*	*Subset B*	*Subset C*	*Subset D*
No of patients	7	12	5	7	4	1	6	9
No of males	6	12	4	6	4	1	5	8
Age (years)	45	44	49	52	45	45	40	54
(mean + range)	(32 59)	(31 56)	(40 56)	(45 61)	(37 48)		(24 60)	(37 65)
Duration of disease	21	19	53	33	9	36	39	77
(months)								
(mean + range)	(1 60)	(2 36)	(1 168)	(2 100)	(1 22)		(2 84)	(3 108)
Severity of angina (NYHA grading) (mean value)	2 1	1 9	2 6	2 3	2 8	3 0	2 4	25
No of episodes of infarction per patient	0 6	1 1	0 6	1 1	0 8	1 0	1 0	19
No of patients with shortness of breath	0	3	0	2	0	0	1	4
No of patients with S_3	0	2	0	2	0	1	1	1
No of patients with S_4	2	7	4	2	1	0	3	5

S_3 = third heart sound S_4 = fourth heart sound NYHA = New York Heart Association (1964)[32]

Methods

Cardiac catheterization was performed in the fasting state Premedication with 10 mg of diazepam and 50 mg of pethidine was given A routine left heart study was made through a per cutaneous puncture of the femoral artery In travascular and intracardiac pressures recorded using a Statham P23 Db bonded strain gauge and an Electronics for Medicine DR 16 photographic recorder with an electronic analog differentiat ing circuit with minimal phase lag or distortion The mid chest level was used as the zero ref erence for pressure measurements

Left ventriculography was performed in the right anterior oblique (RAO) position using a slow injection of 50 ml of 76 per cent Urografin A 9 inch Phillips image intensifier was used and film ing made with a 35 mm Arriflex camera at 48 frames per second Ventricular volumes were calculated at end diastole (EDV) and end systole (ESV) according to the method of Greene and co workers[12] and allowing for magnification Ejec tion fraction (EF) was calculated where

$$EF = \frac{EDV-ESV}{EDV} \times 100\%$$

LV asynergy was calculated from the uniplane ventriculogram in the RAO view The asynergic segment of the LV was measured and expressed as the percentage of left ventricular circum ference which failed to contract normally in this view The mitral and aortic orifices were ex cluded from the measurement We could not al ways distinguish between akinesis, dyskinesis, or asyneresis so that we described total asynergy[13]

The procedure was completed with selective left and right coronary angiography in multiple oblique views using the Judkins method[14 15] A Phillips 6 inch image intensifier and Arriflex 35 mm cine camera were used filming at 32 frames per second on Gevapan 36 film

Critique of methods A fluid filled catheter manometer system was used for pressure mea surements Care was taken to debubble the system and the frequency response was flat to 20 Hz The mean pressures over several respiratory cycles were calculated

The injection of a large bolus of contrast medium into the LV alters circulatory dynamics Angiograms which were influenced by ventricu lar ectopic beats were excluded from the analy sis[16 18] Ventricular volumes were calculated from the uniplane RAO cineangiocardiogram using the length diameter method The uniplane meth od for quantitative angiography correlated closely with biplane methods but assumes that

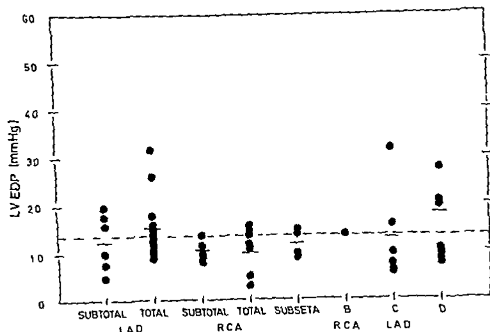


Fig 1 Left ventricular end diastolic pressure (LVEDP) in the different groups of patients LVEDP is increased in several patients with complete LAD occlusion or with complete obstruction of both RCA + LAD (subset D) The dashed line is the upper limit of normal The mean value for each group is shown. LAD = left anterior descending coronary artery RCA = right coronary artery

the major and minor semi axes of the ventricle are related.[19] This is not true in patients with ventricular asynergy and a multicompartmental model moreover the method excludes abnormalities of wall motion which are not shown with the long axis of the ventricle in profile

Results

The clinical findings are given in Table I The patients were usually young or middle aged males There was no difference in mean age between the different groups studied, but patients with disease of the LAD were often younger and had a shorter history of coronary artery disease Patients with complete obstruction of both the RCA and LAD in contrast were older and gave a longer history of symptoms Double vessel disease was associated with more severe angina pectoris than disease of either vessel alone Patients with single vessel disease (complete occlusion) had had one episode of myocardial infarction and 60 per cent of those with incomplete obstruction of a vessel gave this history When both RCA and LAD were completely occluded patients had usually had two episodes of myocardial infarction

The hemodynamic data is shown in Figs 1 through 3 and the extent of LV asynergy in Fig 4 Statistical analysis of the results is given in Table II Patients with incomplete obstruction of the LAD (subset 1A) had on the average 10 per cent LV asynergy a normal or increased ejection fraction and peak LV dp/dt and a normal LVEDP In complete LAD obstruction (subset 1B) there was 46 per cent LV asynergy a normal or decreased ejection fraction and peak LV dp/dt, and a normal or elevated LVEDP The area of asynergy usually involved the distal two thirds of the anterior surface of the LV and the apex[9] Obstruction of the LAD caused extensive ventricular asynergy In isolated RCA disease the area of asynergy was much *smaller* (subtotal = 0 per cent total = 15 per cent) and the hemodynamics normal. The area of asynergy was limited to the basal or middle thirds of the diaphragmatic surface of the LV

Patients with double vessel disease and bilateral subtotal occlusion (subset 3A) had a normal hemodynamic pattern In patients with complete occlusion of one vessel and subtotal obstruction of the other (subsets 3B and 3C) the picture was similar to that seen in patients with complete occlusion of either vessel alone One patient in subset 3C had impaired LV function he had 100 per cent RCA and 90 per cent LAD obstruction Complete occlusion of both arteries (subset

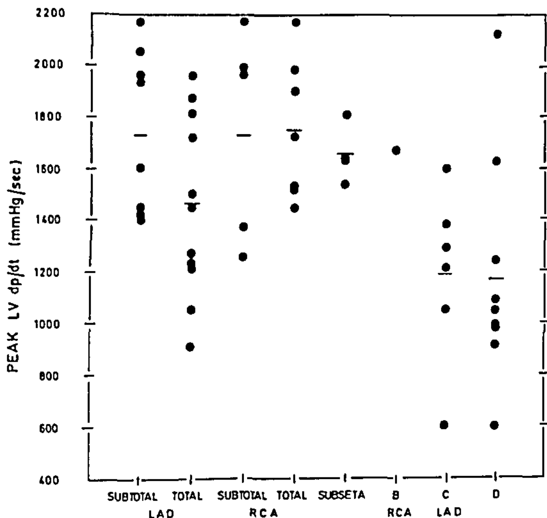


Fig 2 Peak LV dp/dt in the different sets and subsets of patients Peak LV dp/dt is decreased in two patients with complete occlusion of the anterior descending coronary artery (LAD) in one patient with complete right coronary artery (RCA) occlusion + subtotal LAD occlusion (subset C) and in several patients with complete obstruction of both vessels (subset D) It is increased in 10 patients with single vessel disease The mean value for each group of patients is shown

3D) was associated with a large area of ventricular asynergy (Fig 4) and severe impairment of ventricular function The underlying coronary arterial anatomy and the development of collateral vessels seemed to be important in relation to the outcome of infarction Two patients with complete LAD and RCA occlusion (80 and 96 per cent LV asynergy) and severe ventricular dysfunction and cardiac failure had a small circumflex artery and poor collateral circulation In contrast, two other patients with occlusions in almost identical anatomic sites had an extensive collateral network to supply the distal vessel(s) the myocardium in the perfused regions was protected and the patients had a *limited* area of ventricular asynergy without significant depression of left ventricular function

The relationship between percentage LV asynergy and ejection fraction is shown in Fig 5 Patients with a large area of ventricular asynergy had a decreased ejection fraction and this confirms the findings of Feild and co workers[3] and Kitamura and co workers[20]

Discussion

Review of the literature Regional abnormalities of left ventricular contraction (LV asynergy) have been demonstrated in many patients with coronary artery disease[13,21,22] The region of asynergy is reflected on the resting or effort ECG[13,23,24] It is related to the local lesions in the coronary arteries patients with important asynergy often have occlusion of the anterior descending branch of the left coronary artery[13,20,25,26] and asynergy is more common in patients with diffuse coronary artery obstruction,[24] but there are no published studies which quantitate and compare the extent of asynergy and the

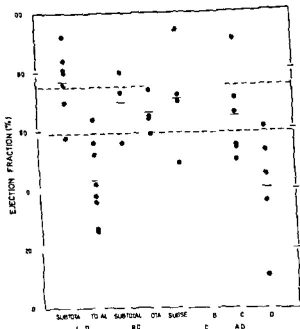


Fig 3 Left ventricular ejection fraction is reduced in seven patients with complete obstruction of the left anterior descending coronary artery (LAD) and in five patients with complete occlusion of the right coronary artery (RCA) + LAD The mean value for each group is shown. The normal range for ejection fraction is shown by the dashed lines.

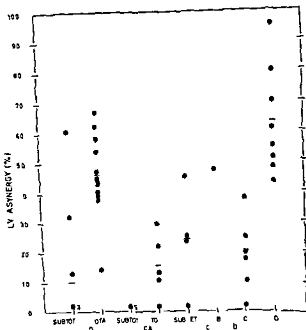


Fig 4 Percentage left ventricular (LV) asynergy in the different syndromes of coronary artery disease Subtotal occlusion of an artery(ies) produces no regional asynergy or mild asyneresis in all but two patients. Complete occlusion of the right coronary artery (RCA) causes a small area of LV asynergy (mean = 15 per cent) but complete anterior descending (LAD) obstruction produces more extensive asynergy (mean = 46 per cent) Complete occlusion of both RCA + LAD (subset D) always leads to a large area of ventricular asynergy (mean = 63 per cent)

hemodynamic abnormality resulting from different pathologic lesions of the coronary arteries

If the area of asynergy is large LV function is abnormal When the noncontractile region exceeds 20 to 25 per cent of the left ventricular internal surface area a normal stroke volume can not be maintained.[27] The area of asynergy is related to LV end diastolic volume and ejection fraction if the area of asynergy is large the end diastolic volume increases and ejection fraction is reduced. Patients with a large area of asynergy also have a high LV end diastolic pressure and low mean velocity of circumferential shortening Compensatory hypertrophy of the remaining myocardium occurs in an attempt to maintain normal overall cardiac function [5,28] Ventricular function improves after excision of the asynergic segment provided that the remaining myocardium is healthy a low preoperative ejection fraction disproportionate to the size of the noncontractile area implies generalized myocardial dysfunction [3,20]

Present study The present study highlights the importance of defining in detail, the pathologic lesion in the coronary arteries when studying the hemodynamics of coronary disease Isolated obstruction of a single coronary artery produces a localized area of myocardial asynergy (15 per cent for RCA and 46 per cent for LAD) The difference in the degree of asynergy between these two groups of patients is noteworthy ($t = 4.33$ $p < 0.001$) Overall ventricular function is normal in RCA disease and normal or slightly depressed in LAD obstruction but this is usually not associated with clinical evidence of cardiac dysfunction Additional incomplete obstruction of the other artery may cause more severe angina but does not alter the hemodynamic pattern

Complete obstruction of two vessels (RCA + LAD) *is associated* with a large area(s) of LV asynergy and depressed LV function which may be severe unless the underlying coronary anatomy and collateral circulation is favorable The patients give a history of two episodes of infarc

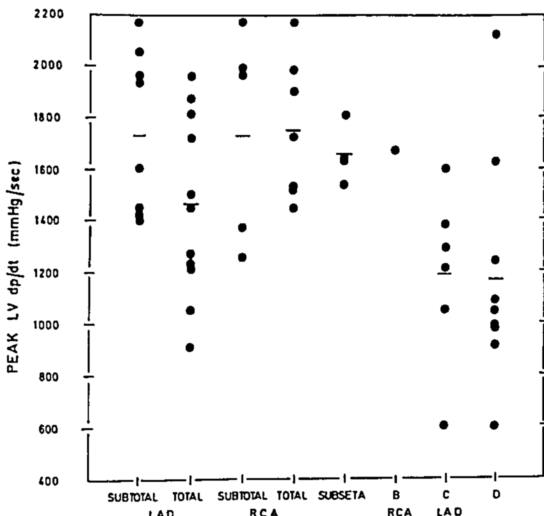


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tion and the price paid is high there is often great reduction in their effort tolerance or frank cardiac failure

Incomplete obstruction of a coronary artery may be associated with severe angina [29,30] It is interesting that in our study several patients with severe subtotal narrowing of an artery had an increased ejection fraction and peak LV dp/dt The patients were normotensive and there was no evidence to suggest hypertrophic cardiomyopathy This may be a compensatory mechanism to increase coronary blood flow to ischemic myocardium but a hypercontractile ventricle has increased myocardial oxygen demand. The metabolic state of the ventricle may therefore be finely balanced in these patients and this may explain how a small change in oxygen supply or demand might precipitate severe angina or acute myocardial infarction

The anatomy of the coronary arterial tree varies enormously in different individuals The RCA is dominant in 90 per cent of patients and from it arises the posterior interventricular artery and branches to the diaphragmatic surface of the left ventricle [31] In 10 per cent of the patients the circumflex artery is dominant in these circumstances RCA occlusion would be expected to cause a small area of asynergy Differences in the basic coronary arterial anatomy may explain ventriculographic and hemodynamic differences between patients in the same set or subset

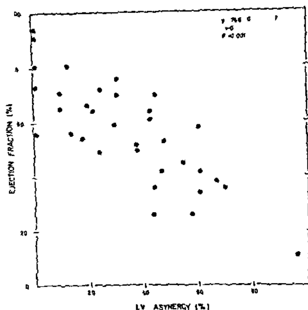


Fig 5 Linear relationship between percentage left ventricular (LV) asynergy and LV ejection fraction.

Summary

The percentage of left ventricular (LV) asynergy was measured in patients with isolated narrowing or obstruction of the right coronary artery (RCA) the anterior descending branch of the left coronary artery (LAD) or a combination of these lesions.

Incomplete obstruction of a vessel was not associated with important asynergy Isolated obstruction of the LAD caused asynergy of the distal two thirds of the anterior wall and apex of the LV and 46 per cent asynergy Isolated obstruction of the RCA caused asynergy of the middle or basal thirds of the diaphragmatic surface and 15 per cent asynergy Double vessel disease produced a combination of the individual lesions and total obstruction of both arteries caused extensive asynergy

In each patient the extent of asynergy was modified by the underlying coronary artery anatomy and the collateral circulation Ejection fraction was related to the percentage of LV asynergy

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Table II Statistical analysis

			LAD		RCA		RCA + LAD			
			Subtotal	*Total*	*Subtotal*	*Total*	*Subset A*	*Subset B*	*Subset C*	*Subset D*
Percentage LV asynergy										
LAD	Subtotal	t value								
		p	—							
	Total	t value	3 12							
		p	<0 01	—						
RCA	Subtotal	t value	1 86	7 21						
		p	ns	<0 001	—					
	Total	t value	0 39	4 33	2 92					
		p	ns	<0 001	<0 05	—				
RCA + LAD	Subset A	t value	0 30	2 56	2 91	0 85				
		p	ns	<0 05	<0 05	ns	—			
	Subset B	t value								
		p	—	—	—	—	—	—		
	Subset C	t value	0 09	3 99	3 16	0 47	0 51			
		p	ns	<0 05	<0 05	ns	ns	—	—	
	Subset D	t value	4 30	2 65	8 13	5 58	3 76		5 40	
		p	<0 001	<0 05	<0 001	<0 001	<0 01	—	<0 001	—
Peak LV dp/dt										
LAD	Subtotal	t value								
		p	—							
	Total	t value	1 70							
		p	ns	—						
RCA	Subtotal	t value	0 07	1 43						
		p	ns	ns	—					
	Total	t value	0 02	2 01	0 08					
		p	ns	ns	ns	—				
RCA + LAD	Subset A	t value	0 61	1 09	0 40	0 66				
		p	ns	ns	ns	ns	—			
	Subset B	t value								
		p	—	—	—	—	—	—		
	Subset C	t value	2 78	1 49	2 45	3 26	2 60			
		p	<0 05	ns	<0 05	<0 01	<0 05	—	—	
	Subset D	t value	2 71	1 54	2 32	2 96	2 05		0 05	
		p	<0 05	ns	<0 05	<0 05	ns	—	ns	—
Ejection fraction										
LAD	Subtotal	t value								
		p	—							
	Total	t value	5 35							
		p	<0 001	—						
RCA	Subtotal	t value	0 98	2 97						
		p	ns	<0 05	—					
	Total	t value	1 96	3 11	0 59					
		p	ns	<0 05	ns	—				
RCA + LAD	Subset A	t value	0 70	3 06	0 13	0 59				
		p	ns	<0 05	ns	ns	—			
	Subset B	t value								
		p	—	—	—	—	—	—		
	Subset C	t value	1 76	2 82	0 51	0 12	0 63			
		p	ns	<0 05	ns	ns	ns	—	—	
	Subset D	t value	4 70	0 30	2 59	2 75	2 72		2 59	
		p	<0 001	ns	<0 05	<0 05	<0 05	—	<0 05	—

Case reports

Myocardial infarction without obstructive coronary artery disease

Albert N Brest, M D
Leslie Wiener M D
Hratch Kasparian M D
Peter Duca M D
James J Rafter M D
Philadelphia, Pa.

In most cases myocardial infarction evolves from underlying coronary artery disease usually atherosclerotic in origin However in recent years scattered reports have appeared, describing instances of myocardial infarction occurring in the absence of any coronary abnormality[1-8] The diagnosis in most of these latter cases has depended on normal coronary angiographic findings and this has invited criticisms—especially the contention that coronary arteriography may fail to disclose an occlusion of a small coronary branch[9] In addition there has been understandable clinical confusion between these latter cases and those instances of myocardial ischemia due to myocardial metabolic defects[10,11] or to disease of the small coronary arteries [12] It is becoming increasingly clear nonetheless that myocardial infarction can indeed occur in the absence of large or small vessel coronary disease or other discernible abnormalities The present report describes five additional cases of myocardial infarction without obstructive coronary disease and reviews the literature relative to this subject.

Case reports

Case 1 J S a 35 year-old black man, was hospitalized with a complaint of severe retrosternal chest pain. The pain was accompanied by marked diaphoresis lasting eight hours and relieved finally after several injections of meperidine. His prior health had always been good. Family history was unremarkable Systemic review was negative

From the D vision of Card ology J E son M dical College Philadelphia Pa

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Reprint requests to Albert N Brest, M D Divi ion of Ca d logy Jefferson Medic l College Ph ladelphia, Pa. 19107

Physical examination on admission was unremarkable except for sinus tachycardia (115 beats per minute)

Serial enzyme determinations showed elevated values for creatinine phosphokinase (CPK) for three days glutamic oxaloacetic transaminase (GOT) for four days and lactic dehydrogenase (LDH) for five days Serial electrocardiograms (ECGs) were indicative of transmural inferolateral myocardial infarction (Fig 1)

Selective coronary arteriography (Sones technique) was performed three months later No coronary occlusive disease was demonstrated (Fig 2) Left ventriculography was normal Results of other studies included. hemoglobin, 16 4 Gm. per 100 ml hematocrit 47 per cent blood urea nitrogen (BUN) 12 mg per 100 ml uric acid, 4 4 mg per 100 ml. cholesterol 260 mg per 100 ml triglyceride 118 mg per 100 ml normal lipoprotein pattern normal glucose tolerance te t and normal chest x rays

During the 18 months following acute myocardial infarction the patient has remained asymptomatic (despite working as a manual laborer) and physical findings have been unremarkable.

Case 2 This 35 year-old white man was hospitalized with severe substernal chest pain of five hours duration. The non radiating chest pain was accompanied by diaphoresis and required several injections of morphine for relief His previous health had been good. Family history was unremarkable Systemic review was negative

Physical examination on admission was negative except for many premature beats. ECG monitoring revealed frequent ventricular premature contractions occa ionally coupled with short runs of ventricular tachycardia. The ectopic rhythm was controlled with lidocaine administered intravenously Injections of lidocaine were required intermittently during the first 24 hours following admission

Serial enzyme studies showed elevated values of GOT for three days, and LDH for four days Serial ECGs were indicative of transmural inferolateral myocardial infarction.

Selective coronary arteriography (Sones technique) was performed five months later No coronary occlusive disease was demonstrated Left ventriculography was normal Results of other studies included hemoglobin 16 5 Gm. per 100 ml hematocrit, 45 5 per cent BUN 15 mg per 100 ml.

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Fig 2 Coronary arteriograms from case 1 reveal normally patent left and right coronary arteries.

one or more of the three major extramural coronary arteries Generally the coronary disease is atherosclerotic in origin but on occasion the coronary abnormalities are due to congenital inflammatory, collagen or other disorders Myocardial infarction occurs occasionally in patients with normal coronary arteries as the result of underlying cardiac disease e g aortic stenosis, or of underlying systemic disorder e g hypotension anemia or pulmonary embolism.[17] In these latter cases the myocardial infarction is usually subendocardial in location Case reports such as those described herein indicate that myocardial infarction may also occur in patients with normal coronary arteries and without any evidence of underlying cardiac or systemic disease

Glancy and co workers[4] recently reported acute transmural myocardial infarction in two young patients with normal coronary arteriograms Cases 1 3 and 4 described in the present report are very similar clinically In each of these five cases the evidence that acute infarction occurred seems indisputable i.e characteristic chest pain was accompanied by ECG evidences of acute transmural myocardial infarction and by typical serum enzyme changes Furthermore none of these five patients had experienced angina pectoris either before or after infarction In addition none had any of the usual coronary risk factors i e diabetes hypertension lipid abnormality or family history of premature coronary arterial disease

In addition to the aforementioned patients Campeau and associates[1] described six other individuals who had good evidence of acute myocardial infarction absence of angina before

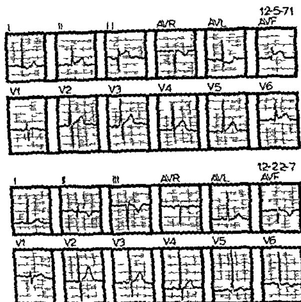


Fig 3 ECGs from case 5 show evolutionary changes of acute transmural inferolateral myocardial infarction

or after infarction and arteriographically normal coronary arteries In some however the infarction was subendocardial in location and, in a few there were no permanent ECG changes

There are still other reports of patients with myocardial infarction and arteriographically normal coronary arteries who have experienced, in addition an anginal syndrome occurring before and/or after the infarction.[3,16] Furthermore there are reports of patients with recurrent myocardial infarction despite arteriographically normal coronary arteries[7] Case 2 in the present series fits into the latter category Conceivably these various patients may all fit

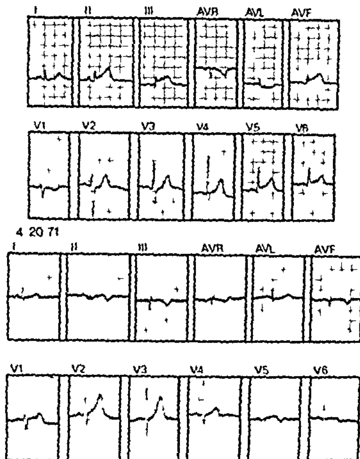


Fig 1 ECGs from case 1 reveal evolutionary changes of acute transmural inferolateral myocardial infarction

uric acid 5 5 mg per 100 ml cholesterol 255 mg per 100 ml triglyceride 110 mg per 100 ml normal glucose tolerance test and normal chest x rays

During the subsequent 13 months following acute myocardial infarction the patient remained asymptomatic and the physical findings normal Then following an evening of excessive alcoholic intake he experienced acute upper abdominal pain and was hospitalized for treatment After several hours of abdominal discomfort he suddenly developed cardiac arrest and all attempts at cardiac resuscitation were unsuccessful Postmortem examination disclosed evidences of acute pancreatitis Cardiac examination revealed scarring of the inferior myocardium consistent with old infarction and histologic evidences of early acute anterior myocardial infarction The coronary arteries were free of any occlusive disease and did not contain any thrombi

Case 3 This 40 year old white man a physician was hospitalized with a complaint of left ulnar pain associated with vague chest discomfort which waxed and waned The ulnar and chest discomfort lasted approximately 12 hours His prior health had been good Family history was unremarkable Systemic review was negative

Physical examination on admission was unremarkable

Serial enzyme studies showed elevated values for CPK and GOT for three days Serial ECGs were indicative of transmural inferolateral myocardial infarction The patient s hospital course was uncomplicated

Selective coronary arteriography (Sones technique) was performed six months later Cinearteriography did not reveal any occlusive disease left ventriculography was normal. Results of other studies included hemoglobin, 15 1 Gm. per 100 ml hematocrit 44 5 per cent fasting blood sugar 105 mg per 100 ml BUN 15 mg per 100 ml uric acid, 5 4 mg per 100 ml cholesterol 220 mg per 100 ml triglyceride 32 mg per 100 ml normal lipoprotein pattern and normal chest x rays

During the six months following acute myocardial infarction the patient has remained asymptomatic.

Case 4 This 28 year old white man was hospitalized with a complaint of severe chest pain which radiated into the left arm and neck The pain lasted two hours, was relieved by parenterally administered meperidine and did not recur subsequently His prior health had always been good

Physical examination on admission was unremarkable except for obesity

CPK was elevated on the first hospital day additional CPK determinations were not done GOT was elevated on the first three hospital days and LDH on the second and third days Serial ECGs were indicative of transmural inferolateral myocardial infarction

Selective coronary arteriography (Sones technique) and left ventriculography were performed five months later Both findings were normal Results of other studies included fasting blood sugar 101 mg per 100 ml BUN 21 mg per 100 ml uric acid 8 6 mg per 100 ml cholesterol 153 mg per 100 ml and normal chest x rays

During the six months following acute myocardial infarction the patient has remained asymptomatic

Case 5 W M a 38 year old white man was hospitalized with acute severe epigastric and lower retrosternal chest pain, crushing in character and associated with diaphoresis. He had been examined on two occasions in the past year for gas pain and a pleuritic type of left chest pain. His prior health had otherwise been good. He had no family history of heart disease

Physical examination on admission was normal except that he appeared to be in acute distress

ECGs (Fig 3) showed a typical evolutionary pattern of transmural inferolateral myocardial infarction Serial enzymes including CPK GOT and LDH were transiently elevated for three days The blood sugar was slightly elevated (125 mg per 100 ml) but results of other laboratory studies were normal

The patient recovered from this illness uneventfully but continued to have intermittent nonspecific chest pain Coronary arteriography and left ventriculography were performed six months later The right and left coronary arteries viewed in multiple projections were normally patent (Fig 4) The left ventriculogram (Fig 5) showed an abnormal contraction pattern with akinesis of a large portion of the posterior wall This abnormality corresponded with the ECG evidence of a transmural inferior wall myocardial infarction.

Discussion

Studies at necropsy[13 15] and studies employing coronary arteriography[2 16] indicate quite clearly that the great majority of patients with transmural or subendocardial infarction have high grade (usually at least 75 per cent) narrowing of





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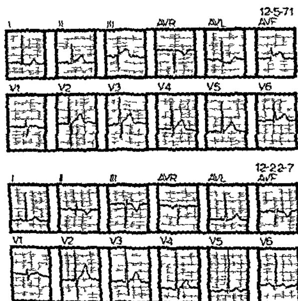


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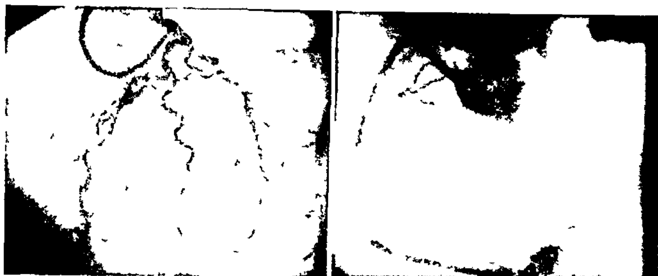


Fig 4 Coronary arteriograms from case 5 show normally patent left and right coronary arteries



Fig 5 Left ventriculograms from case 5 reveal akinesis of the posterior wall of the left ventricle (left diastole right systole)

into the clinical spectrum of a single disorder However, it seems more likely that more than one disorder i e various etiologies will be implicated

Glancy and associates[4] suggested that embolization or in situ thrombosis with subsequent clot lysis could explain the occurrence of myocardial infarction in patients with arteriographically normal coronary arteries A report by Bruschke and colleagues[7] has provided some support for their hypothesis The latter authors reported five patients who had a well documented acute myocardial infarction and in whom selective coronary arteriography failed to disclose any obstructive lesions of the coronary arteries Their second case was of particular interest insofar as a possible etiologic mechanism is concerned The latter patient sustained a second myocardial infarction and, whereas the first coronary arteriography was normal a second arteriographic study revealed total occlusion of the anterior descending artery A third arteriography performed six months later disclosed partial recanalization of the obstructed artery These findings pointed toward a primary thromboembolic process as the possible etiology On the basis of their findings Bruschke and co authors[7] recommended that the very absence of atherosclerotic narrowings despite clinically convincing evidence of acute myocardial infarction or ischemia should raise the suspicion of a thromboembolic process and therefore should be regarded as a prime indication for anticoagulant therapy

A report by Himbert and associates[19] also implicated a thrombotic process in the genesis of nonatherosclerotic myocardial infarction These authors described three cases of primitive coronary thrombosis involving exclusively the anterior descending artery At necropsy the arteries appeared to be free from atherosclerosis but other slight nonobstructive changes of the vessel wall were noted in all three cases Conceivably these changes which in some cases might escape recognition by coronary arteriogra

phy could provide a substrate for the formation of platelet aggregates and subsequently lead to thrombosis

Primary thrombosis undoubtedly accounts for unexplained myocardial infarction in some patients but this mechanism obviously cannot explain the genesis in all such cases Case 2 in the present series is pertinent in this regard This patient succumbed to cardiac arrest and although early evidence of a (second) acute myocardial infarction was found at autopsy necropsy examination of the coronary arteries failed to reveal any evidence of thrombosis

Myocardial necrosis without coronary occlusion has been observed in epileptic patients[20] this unusual complication has suggested coronary artery spasm as a possible basis for myocardial infarction The coexistence of pulmonary embolism and myocardial infarction in patients without underlying coronary disease[17] also supports acute coronary constriction as a possible etiologic factor Although the occurrence of coronary artery spasm has been recognized repeatedly since the inception of coronary arteriography this finding has been attributed usually to local trauma from the catheter However we have observed at least two cases where coronary spasm and delayed forward transit of contrast material occurred at areas far removed from the catheter tip Both of the latter two patients were studied because of an anginal syndrome but neither had sustained a myocardial infarction Recently Dhurandher and associates[21] described a patient with variant angina pectoris in whom spasm of a coronary artery with extremely poor distal runoff was demonstrated during coronary arteriography coincident with the onset of chest pain In addition Cheng and coworkers[22] reported an instance of acute inferior wall myocardial infarction which apparently resulted from a severe spasm during coronary arteriography of the left circumflex artery Although the precise role of coronary artery spasm in the genesis of myocardial infarction without occlusive coronary disease is uncertain further study is clearly warranted.

The over all incidence of myocardial infarction without coronary artery disease appears to be small but the increasing application of coronary arteriography undoubtedly will identify many more such patients Since the etiology in most of these cases is unknown the prognosis is equally unclear Some of these patients will have additional infarctions but, even in the absence of recurrent infarction the outlook in some of these individuals will be influenced by significant residual myocardial dysfunction resulting from the initial attack Such dysfunction was clearly evident in our fifth patient and has been reported also in other cases[4,7,8]

Myocardial ischemia and necrosis in the absence of obstructive coronary artery disease have been related in some cases to abnormal hemoglobin oxygen dissociation Eliot and Bratt[10] described three such patients who sustained subendocardial infarction In each of the three subsequent postmortem examination revealed patent and apparently normal coronary arteries despite the presence of one to three subendocardial infarcts of the left ventricle in none was there any evidence of small coronary artery disease found in histologic sections directly adjacent to the infarcted areas or in random sections from other uninvolved areas It appears that most if not all of the patients with this disorder experience an anginal syndrome the myocardial hypoxia is generally supported by ST segment depression in the exercise ECG and by myocardial lactate production during pacing induced tachycardia However such abnormalities of hemoglobin oxygen dissociation have been found in only a small percentage of patients with myocardial hypoxia and normal coronary arteriograms[23] Thus although the incidence of this disorder among patients with myocardial infarction and arteriographically normal coronary arteries is presently unknown it is likely to be small

Disease of the small coronary arteries i.e those distal coronary vessels which are 0 1 to 1 mm. in diameter has been alleged to cause myocardial degeneration myocardial fibrosis myocardial infarction myocardial insufficiency cardiac enlargement and ventricular hypertrophy[12] Whereas the occurrence of small foci of myocardial degeneration and scarring has been substantiated, the other associations are less clearly defined. Furthermore it seems quite likely that the type of case described in this report, i e transmural myocardial infarction is rarely if ever due to small vessel coronary disease

Finally it seems noteworthy that each of the

five patients in the present series sustained an acute inferolateral myocardial infarction However, other authors[1-8] have reported cases of acute anterior, anteroseptal, anterolateral, and posterior myocardial infarctions in the absence of obstructive coronary artery disease Accordingly, the common location of the infarctions reported in the present group appears to be merely a curious coincidence

Summary

The present report describes five cases of transmural myocardial infarction occurring in patients without occlusive coronary artery disease or other discernible abnormalities It is apparent from these cases and others described in the literature that such patients may present with or without angina and in some, the clinical course will be complicated by recurrent infarction and/or significant residual myocardial dysfunction At present the exact incidence and natural history of this syndrome is unclear Undoubtedly the increasing application of coronary arteriography will identify many more such patients Delineation of the genesis and the full clinical spectrum of myocardial infarction without coronary artery disease warrants further investigative attention

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Single primitive ventricle with D-transposition of the great vessels and atresia of the left A-V valve

Report of a case

A Cabrera M D
J I Azcuna M D
F Bilbao M D
Bilbao, Spain

Until recently the concept of the type A single ventricle[1] or single primitive ventricle[2] implied either the permeability of the two auriculo ventricular (A V) valves or the presence of a common A V valve In 1970 Quero[3] published a report of a case of a single ventricle with atresia of the left A V valve and normally positioned great vessels (Holmes heart) More recently the same author[4] published another case of a single ventricle with atresia of the right A V valve and L transposition

The aim of this paper is to report a case of type A single ventricle with atresia of the left A V valve and D transposition of the great vessels a morphologic situation which to our knowledge has not been described before

Case report

Case 1 A very ill 12 day old boy was admitted to the hospital with generalized cyanosis, severe dyspnea and hypotonia which had been gradually increasing since the sixth day of life The birth weight was 4,330 grams.

Physical examination revealed a cyanotic baby in severe *respiratory distress.* The cardiac rate was 130 beats per minute Positive findings included a palpable thrill a Grade 3 4/6 systolic mesocardiac murmur disseminated pulmonary râles, and an enlarged liver Peripheral pulses were weak but palpable in all four extremities

Radiologic examination showed a marked cardiac hypertrophy with a narrow arch and pulmonary hypervascularization.

From the Department of Pediatrics, Divisions of Pediatric Cardiology (Dr Cabrera) Radiology (Dr Azcuna) and Pathology (Dr Bilbao) Hospital Infantil de l Seguridad Social E. Sotomayor Bilbao Spain

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Reprint requests to A. Cabre a, M D Alameda de Recalde 35 b-?o Bilbao, Spain

The electrocardiographic (ECG) findings were as follows. *sinus rhythm* rate of 150 beats per minute AQRS axis at +90 P waves of 2 5 *mm* in D_2, RS with T negative in Lead V_1 RS morphology from V_2 to V_5 and R with T negative in V_6



Fig 1 A P view of the heart. The aorta is anterior and to the right of the pulmonary artery The left coronary artery comes from the left lateral sinus *A.Aorta,* aorta artery-*Coart.P D* preductal coarctation *A.pul.* pulmonary artery-*LP* left pulmonary artery *LC,* left coronary artery

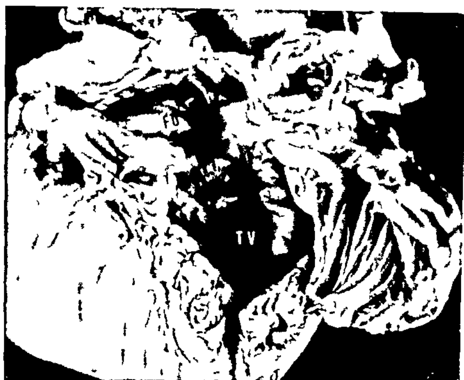


Fig 2 View of the right atrium The pectineal muscle the foramen ovalis and the right A V valve can be easily appreciated *FO* foramen ovalis *RA* right atrium *TV* tricuspid valve



Fig 3 General view of the single ventricle the rudimentary chamber and the great vessels The A V valve is in fibrous continuity (asterisk) with the pulmonary valve The left ventricle communicated with rudimentary chamber through the bulboventricular foramen The aorta can be seen on top of the supraventricular crest *LC* left coronary artery *PM* papillary muscle *RA* right atrium *P* pulmonary valve *LV* left ventricle *F* bulboventricular foramen *CS* supraventricular crest *A* aorta

Emergency treatment was carried out immediately but the baby died with cardiac failure two days after admission

Pathology Gross examination revealed the presence of a visceroatrial situs solitus with the cardiac apex on the left side The aorta was anterior and *to the right of the pulmonary artery* The diameter of both vessels was similar (Fig 1)

A very large right atrium morphologically normal communicated with a large triangular ventricle through a three leaflet A V valve The ventricle had trabeculation only in *its* apical portion the rest of it being smooth A patent foramen ovale was present (Fig 2) The pulmonary artery originated from this ventricle and was in continuity with the A V valve



Fig 4 Partial view of the rudimentary chamber The bulboventricular foramen the supraventricular crest and the aorta can be seen with their three Valsalva sinuses (*R* right *P* posterior *L* left) and the left coronary artery (*LC*) *F* bulboventricular foramen *CS* supraventricular crest *A* aorta *R* right Valsalva sinus *P* posterior Valsalva sinus *L* left coronary artery

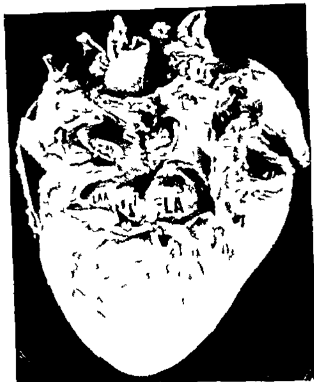


Fig 5 View of the left atrium The auricular appendage is shown on the left the blind fossa (asterisk) corresponding to the mitral atresic valve *LA* left atrium *LAA* left auricular appendage *PV* pulmonary veins

The ventricle communicated with a rudimentary chamber located on its right side by means of a bulboventricular foramen (Fig 3) This chamber was formed by the distal conus and was the origin of the aorta situated in D transposition (Fig 4) The coronary arteries originated from the posterior and left lateral Valsalva sinuses

The left atrium was of normal morphology and small in size In the area corresponding to the left A V valve there was a blind fossa (Fig 5)

A preductal coarctation was also present with a patent ductus.

Discussion

The type A single ventricle[1] or single primitive ventricle[2] can occur in three forms according to the position of the great vessels normally related, in L-transposition or in D transposition This definition implies either the permeability of the two A V valves or a common A V valve In 1970 Quero[3] introduced the concept of a single primitive ventricle with atresia of one A V valve and this only if the ventricle present is the homologue of the atretic valve Under this new concept the three previously described varieties of a single primitive ventricle could occur theoretically associated with atresia of one A V valve Quero[3,4] has already described two of these varieties one with normally positioned vessels (Holmes heart) and the other with L transposition The case we report here represents the third possibility the large egg shaped ventricle is smooth in its upper part and communicates through a bulboventricular foramen with a rudimentary chamber situated on its right This rudimentary chamber is formed by the distal conus It represents the origin of the aorta which is in D transposition The coronary arteries are in the usual D transposition situation The left atrium is totally separated from the right one and receives the pulmonary veins the left auricular appendage is present.

Cases similar to those reported by Quero and the one reported here were not considered as cases of single ventricle until recently and were interpreted as atresias of an A V valve with two ventricles, one of them hypoplastic It is impor

tant to emphasize that in cases of isolated A V valve atresia the hypoplastic ventricle is the homologue of the atretic valve We believe therefore that our case really represents a variety of type A single ventricle or single primitive ventricle with D transposition and atresia of the left A V valve—a condition not previously reported

Summary

We have reported a case of a cyanotic newborn infant with left ventricular hypertrophy and cardiac insufficiency He died at 14 days of age and the pathologic study revealed the existence of a single morphologic left ventricle with D transposition and atresia of the left A V valve The existing ventricle was the homologue of the atretic valve

This case, together with the other two cases described in the literature confirm the existence of a type A single ventricle or single primitive ventricle with atresia of an A V valve

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Clinical-pathologic conference

John R Dainauskas M D
Armando Susmano M D
Maurice L Bogdonoff M D
Chicago Ill.

Clinical summary

A 56 year old retired, white fireman had been in good health until developing signs and symptoms of congestive heart failure two years before admission to this hospital At that time he was hospitalized elsewhere because of severe pedal edema 30 pound weight gain and shortness of breath. He was treated with heart and water pills and improved, but was again hospitalized a month later with pneumonia Since that time he quit working because of increasing fatigue and shortness of breath even when climbing one flight of stairs or walking one half block There was a history of hypertension with occasional palpitations but further particulars about duration severity or treatment were not available The patient also had noted dry skin pruritis, periorbital edema and increased sensitivity to cold There was no history of chest pain paroxysmal nocturnal dyspnea intermittent claudication or orthopnea. Apparently his speech was slow and mentation had deteriorated. He was taking crystodigin (0 2 mg four times per week) Lasix (80 to 160 mg per day depending on the degree of ankle edema) aminophylline (1½ grams three times a day) and Zyloprim (100 mg three times a day) He stopped smoking but he had a 90 pack per year history of cigarette smoking

On admission the vital signs were blood pressure 110/70 mm Hg pulse 50 to 60 per minute irregularly irregular respirations 16 per minute and temperature 97 F There was bilateral, periorbital edema Dry cool, and peeling skin with cracks was described. The skin of the lower extremities was shiny waxy and pigmented, but there was no edema The thyroid was freely movable slightly enlarged, and the right lobe was larger than the left. The chest was clear to auscultation and percussion The PMI was in the sixth intercostal space at the anterior axillary line S_1 was normal and louder than S_2, but both appeared distant There was no S_3 S_4 or opening snap A harsh low pitched Grade III/VI pansystolic murmur was heard best at the lateral sternal border It radiated to the axilla and toward the pulmonic area Veins in the neck were distended. The peripheral pulses were normal in the upper and decreased in the lower extremities The liver had a span of 11 cm and was palpated with some pulsations 4 cm. below the right costal margin Fluid wave was not described. The motor and sensory functions were intact, but his speech was described as slow and slurred, and his voice as husky Reflexes were generally diminished. There was no peripheral edema

Cardiac catheterization showed the following pressures in millimeters of Hg RA mean pressure 17 pulmonary artery, 55 systolic and 32 diastolic with a mean of 40 and a PA wedge of 28 LV 93 systolic and 28 end diastolic and aortic 93 systolic and 72 diastolic The cardiac index was 0 83 L per minute per square meter The A V oxygen difference was 10 4 vol. per cent The total systemic pulmonary and pulmonary vascular resistance (dynes/sec /cm ^{5}) were 3 904 1 928 and 578 respectively The metabolic rate was ~30 per cent The respiratory rate was 12 per minute heart rate 72 per minute and the O_2 consumption index was 86 ml. per minute per square meter Selective LV cine showed a very large dilated chamber with minimal contractility and large end systolic volume A mild to moderate pericardial effusion was noted.

The patient was placed on a cardiac monitor and Cytomel (5 μg per day) therapy was started. The next day he developed severe pulmonary

From the Departments of Pathology Medicine and Radiology Rush Presbyterian-St. Luke's Medical Center Chicago.

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Reprint requests to: Dr J hn R Da nauskas, Department of Pathology Rush Presbyterian-St. Luk s Medical Center 1753 W Congress Pa kw y Chicago Ill. 60612.



Fig 1 Frontal film of four position series There is marked generalized enlargement of cardiac shadow Pulmonary vasculature shows redistribution There is moderate basilar pulmonary edema with pleural effusion

edema and hypotension Cytomel was discontinued and intravenous digoxin and Lasix increased the blood pressure and decreased the pulmonary edema Then, the patient developed ventricular irritability with 8 to 9 PVC s per minute Questionable ascites but not peripheral edema were described Serum K at that time was 3 0 mEq per liter He died after a cardiorespiratory arrest about two weeks after admission

On admission the hemogram showed a hemoglobin of 13 1 Gm, hematocrit 41 5 RBC, 4 95 million, and WBC, 11,600 with a differential count of 49 polys 33 bands, 12 lymphocytes 5 monocytes, and 1 basophil The platelet count was 62 000 Repeated platelet counts were within normal limits The RBC indices were normal The electrolytes showed Na, 142 K, 3 3 Cl 97 and CO_2 28 0 mEq per liter Calcium was 9 8, phosphorus, 4 4, BUN, 25 creatinine 1 4 mg per cent, CPK 34, ICD 80 SGOT, 28 LDH 590 SGPT, 5, alkaline phosphatase, 4 1 units and uric acid, 9 7 mg per cent Postprandial glucose was 113 mg per cent Total cholesterol was 223 mg per cent Leucine aminopeptidase (LAP) was 194 9 units The plasma cortisol was 25 4 mg per cent, urine 17 OH corticosteroids, 5 8 mg per 24 hours, T_3 uptake, 28 per cent PBI, 2 5 mg per cent T_4 by Murphy Pattee 2 4 μg per cent TSH 120 in μml Immunologic studies showed presence of microsomal antibodies and antibodies to the second colloid antigen Immunoglobulin electrophoresis showed IgG, 5 48 mg per cent, IgA 1 19 mg per cent IgM, 0 36 mg per cent and IgD, 0 06 mg per cent The urinalysis showed specific gravity of 1 006, pH, 6 0, and no protein sugar, or ketone bodies The spun sediment contained no cells

Discussion

DR SUSMANO In summary, we are confronted with the clinical picture of a 56 year old man with a two year history of intermittent and progressive congestive heart failure who has also developed dry skin, increased sensitivity to cold, and slurred speech with a husky voice We have heard about his physical findings as well as his hemodynamic and biochemical abnormalities. Before proceeding with a detailed analysis of all these data, I would like to see the chest x rays.

DR BOGDONOFF Four position chest films dated Dec 18, 1972, have demonstrated marked generalized cardiomegaly The aorta is of normal size and the central pulmonary vasculature is normal There is pulmonary vascular redistribution venous and lymphatic distention as well as a small amount of pleural fluid. All are findings of cardiac decompensation I cannot tell how much of this markedly enlarged heart shadow is due to pericardial fluid Portable films dated Dec. 28, 1972 and Dec 30 1972 showed a marked worsening of the heart failure and widespread alveolar edema in addition to the previously noted interstitial edema This marked bilateral pulmonary edema persists on the portable film of Dec 30, 1972 There have been minor changes in the edema with slight "milking" of edema along the right heart border and minimal improvement in the edema adjacent to the hilar region These findings are characteristic of edema due to marked cardiac decompensation The cardiac findings are nonspecific and are compatible with cardiomyopathy with or without pericardial effusion

DR SUSMANO The electrocardiogram on admission showed atrial fibrillation with a slow ventricular response marked intraventricular conduction block with a QRS duration of 0 20 second, and a very low QRS voltage in the standard leads

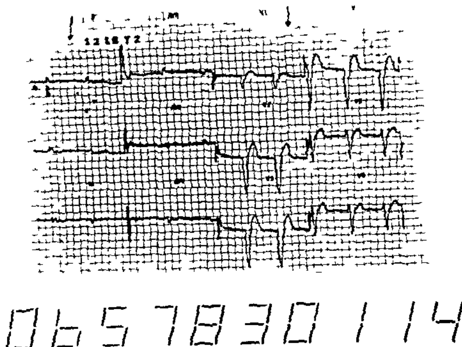


Fig 2. Twelve lead admission electrocardiogram.

Cardiac catheterization revealed mild or perhaps a moderate amount of pericardial effusion. The cardiac index was severely decreased and the LV and RV early and end diastolic pressures were significantly elevated. Selective cineangiocardiogram showed that the left ventricular chamber was markedly dilated, with a significant decrease in left ventricular contractility and very large end diastolic and end systolic volumes All these findings are consistent with the diagnosis of severe cardiomyopathy associated with a mild to moderate degree of pericardial effusion

Let me ignore for the moment the severe abnormalities of the thyroid function We are dealing without any doubt, with a severe case of cardiomyopathy But which one is responsible for it?

On the basis of the history and physical and hemodynamic findings, if we were to follow Drs Mattingly s and Abelman s approach to the cardiomyopathies[1,2] then we could eliminate two important groups the hypertrophic variety whether familial or not, and the obstructive type better known as idiopathic hypertrophic subaortic stenosis (also whether familial or not) No intraventricular pressure gradients were found and the presence of the largely dilated left ventricular chamber with significant decrease in its contractility would easily exclude these two types This patient was apparently hypertensive for several years Although left ventricular hypertrophy with subsequent dilation can be seen in the terminal stages of fixed or malignant hypertension the clinical and radiologic findings are quite different from the ones encountered in this patient. Besides that his hypertension was never severe enough as to require strict therapy Therefore we would not consider this to be the end stage of this disease We should then direct our attention to either the dilated or restricted type of cardiomyopathies In the restricted usually called infiltrative type we should consider amyloid heart disease Amyloidosis can account for up to ten per cent of noncoronary cardiomyopathies It should be considered in relatively older patients who have progressive and intractable types of congestive heart failure which may be associated with skin and mucous membrane lesions purpuric changes nephrosis peripheral neuropathy macroglossia etc None of the symptoms and physical findings just mentioned was encountered in our patient and the electrocardiogram was not associated with QRS abnormalities suggesting the possibility of a dead zone due to myocardial infarction as has been so often seen in patients with cardiac amyloidosis It would also be extremely uncom



Fig 3 *A* Frame of selective left ventricular cineangiogram shows a very large ventricular chamber with markedly increased end diastolic volume *B*, Shows the end systolic volume of the left ventricle Only the posterobasal and outflow tract areas contract although the myocardial contractility is diffusely decreased.

mon for the heart to be radiologically enlarged as much as in this case Usually, it is only slightly enlarged We do not have any evidence to support the possibility of either neoplastic infiltration of the heart, hemochromatosis or glycogen disease the latter exclusively seen in infants and children There was no history or physical findings of involvement of the peripheral muscles therefore myocardial involvement as may occur in heredofamilial neuromyopathic diseases like Friedrich's ataxia, myotonic dystrophy etc can also be excluded. Some patients with the clinical syndrome of constrictive pericarditis have also shown abnormalities in the contractility of the myocardium or what has been called myocardial misuse" as a secondary change to the severe pericardial involvement Occasionally, a patient with constrictive pericarditis may have associated pericardial effusion However in this case the degree of pericardial effusion was probably greater than that encountered in patients who do have primary pericardial disease The syndrome of endocardial fibroelastosis which has been seen in adults can probably be excluded considering our patient's advanced age Certainly other entities that may also involve the endocardium such as endomyocardial fibrosis, as have been observed in Africa should be brought into the differential diagnosis of the restrictive types of cardiomyopathies which I am including as part of the differential diagnosis, but not because I strongly believe this to be a diagnostic possibility in our case

Our patient did not give any history of heavy alcoholic or beer intake and I can possibly exclude them as an etiologic consideration

We now finally come to the last group or the dilated type of cardiomyopathies which are so common in the adult population This form of usually called primary myocardial disease" is also often referred to as the congestive type Numerous etiologies have been suggested for primary myocardial disease and the number of conditions that could be included is quite large ranging from injury to the myocardial muscles secondary to malnutrition, myocarditis unknown toxins, or immunity, trauma toxic agents, specific infections or metabolic abnormalities I like to call primary myocardial disease the type of heart disease where no known etiology can be found. Other types which may produce similar myocardial changes but are secondary to a specific etiology I usually like to refer to as myocarditis which has entered the chronic stage In patients in whom a specific etiology is found, the viral bacterial, mycotic, parasitic, protozoal and rickettsial infections or toxic agents can be the cause of the myocardial injury The damage can also be secondary to a metabolic abnormality As previously mentioned nutritional and electrolyte imbalance and, most commonly severe hypokalemia or anemia can be accompanied by severe myocardial disease Regardless of these different etiologies they may produce common pathologic changes in the so called primary myocardial disease and the findings on physical

examination are commonly the same The jugular venous pressure is elevated and very high V waves can be seen, suggesting the presence of tricuspid incompetence The pulse pressure is usually within normal limits or may be low but, most commonly there is a very narrow pulse pressure Pulsus alternans is also frequent if very clearly sought. There may be no murmurs or just murmurs due to tricuspid or mitral insufficiency which are secondary to ventricular dilation and pulling of the papillary muscles producing valvular incompetence The presence of filling sounds such as prominent third sound or atrial gallops can also be heard. All kinds of electrocardiographic abnormalities have been observed, ranging from changes in voltage particularly low voltage in the standard lead, as well as arrhythmias atrial fibrillation or ventricular arrhythmias and conduction abnormalities, whether of the right bundle or the left bundle branch type First degree A V block has commonly been seen but on many occasions may also be secondary to digitalis therapy Second degree or third degree A V block is extremely uncommon Hemodynamic studies are usually similar with a very low cardiac index and elevated ventricular diastolic pressures. As has been emphasized by Proctor Harvey and colleagues,[3] there is a clinical spectrum of primary myocardial disease ranging from mild to severe degree and the course of the patient s disease will be related to the degree of involvement of the myocardium resulting in death usually in less than two years when the involvement is severe or may evolve into a complete recovery when there is only mild involvement of the myocardium There is a very high incidence of sudden death particularly in the idiopathic type of primary myocardial disease Commonly in patients with primary myocardial disease when no specific etiology can be found, the possibility of viral origin is considered. Coxsackie B virus has been implicated as a common etiologic factor Virus-like particles have been occasionally noted in cardiac tissues of such patients. It is quite possible that once a patient achieved the chronic stage circulating antibodies have significantly decreased and then it is almost impossible to establish a cause and-effect relationship in viral myocardial disease We do not have any real evidence that our patient has had any severe viral infections in the past therefore it would be extremely difficult to relate his myocardial disease with a possible viral etiology and I would consider it very unlikely although I do not have definite proof We do not have any evidence of specific infections such as brucellosis, tuberculosis rickettsial diseases, or toxoplasmosis Therefore infections would not be considered as a potential etiologic factor in this case We also have no evidence for any collagen disease such as rheumatoid arthritis or lupus erythematosus with documented vasculitis which might well be a factor in the development of myocardial disease but again there has been no prior history that may substantiate the possibility of systemic involvement We do not have any history of severe nutritional deficiency and the physical findings did not show an emaciated or cachectic individual nor was he using large amounts of cathartics which may produce extreme hypokalemia and, therefore a hypokalemic cardiomyopathy and we can exclude this possibility

I do believe that by now we have narrowed down most of the diagnostic possibilities I would like to return to what we have concerning real facts in the sense of the history and physical and laboratory findings

Our patient gave a positive history of progressive tiredness somnolence, slow mentation increased intolerance to cold dryness of skin and also typical changes of a 'gravel voice His thyroid studies demonstrated the presence of severely depressed function All of this speaks strongly for myxedema The question posed to us is whether this entity is responsible for the heart disease or not

Many studies most of them case reports have appeared in the literature since Zondek described the condition as a specific entity in 1918 He laid down the criteria of both right and left sided dilation associated with abnormalities of conduction with definite reduction in transverse diameter of the heart following thyroid gland therapy Radiologic enlargement of the heart has been said to be common in myxedema due either to myocardial damage or to the presence of a pericardial effusion or both [4] However other factors such as old age systemic arterial hypertension, and coronary artery disease have been shown in part responsible for the increase in heart size in myxedema Of 53 patients studied by Aber and Thompson [4] 55 per cent were found to have cardiac enlargement, most of whom were

older and had higher systemic hypertension than those patients with normal sized hearts Several of them also had some evidence of ischemic heart disease Conversely, many patients have typical electrocardiographic changes of myxedema heart disease with normal sized hearts and they conclude that this implies the lack of associated hypertension or coronary artery disease

However, as has been pointed out by Kern and co workers,[5] pericardial effusion is a constant early and major factor in the myxedematous heart and the one responsible for the roentgenologic changes in the cardiac silhouette and not due to myocardial failure since in general it responds to thyroid therapy alone

Our patient has had intermittent episodes of heart failure The question as to whether or not myxedema heart can evolve into heart failure has been disputed and questioned for many years after Fahr reported the occurrence of heart failure in this disease Hemodynamic studies have shown that the cardiac output is significantly depressed and parallel in general to the decrease in oxygen consumption While A V differences have been observed to be within normal limits or slightly wider the cardiac output may be depressed out of proportion to the oxygen demands of the body This represents strong evidence of damage to the heart and of circulatory insufficiency according to the studies by Ellis and co workers[6]

Studies performed by Graettinger and co workers[7] have shown the cardiac index to be considerably below normal but an adequate increase occurred during bicycle exercise Right atrial pressures were elevated at rest and the right ventricular pressures had a diastolic dip with elevated end diastolic pressures, findings which were attributed to pericardial effusion rather than to myocardial disease Their patients had a low normal heart rate with a significant decrease in stroke volume at rest This was in sharp contrast with patients who did have primary myocardial disease and who were in congestive failure Their oxygen consumption at rest and the basal metabolic rates were normal or elevated and the cardiac output was significantly lower than in patients with myxedema or normal persons Furthermore the heart rate was faster the A V differences much wider at rest and the cardiac output did not increase or decrease during exercise

Our patient had severe myocardial disease manifested by significantly wide A V difference markedly decreased cardiac output elevated end diastolic pressures in both ventricles, low stroke volume, and diffuse decreased contractility by selective left ventricular cineangiogram. However, he did have a normal respiratory rate a slow ventricular rate, a very low oxygen consumption, and a low metabolic rate which is exactly the opposite of what one would expect if this degree of myocardial failure was due to primary myocardial disease

As stated by Ellis and co workers,[6] there appears to be no uniformity in the response of the cardiovascular system to myxedema

It is also true that patients who have been in intractable heart failure were improved in the past by being made myxedematous. Although this appears to be a paradox, total ablation of the thyroid seems to benefit the heart by lessening the circulatory demands through a reduction in the oxygen consumption and, therefore, decreasing the metabolic needs the cardiac output, and the cardiac work This also could relieve angina pectoris

In a study of 20 patients with myxedema where 16 had large hearts and only seven were clinically indistinguishable from cardiac failure, pulse pressure response to the Valsalva maneuver showed that apparently only one of the patients was in cardiac failure[8] It was assumed, therefore by McBrien and Hindle[8] that myxedema in itself does not cause heart failure and, if it occurs it is the result of other disease, usually ischemic This work evidently is at variance with the observation of other authors where myxedema and heart failure have been observed in the absence of coronary artery disease Furthermore, a case report was published by Monroe and Fearrington[9] of a patient with severe myxedema and marked cardiomegaly who continued to have massive cardiomegaly after all pericardial effusion had been removed. The venous angiocardiogram showed the cardiac enlargement to be due primarily to left ventricular dilation demonstrating then that the persistent cardiomegaly was due to myxedematous cardiomyopathy

Finally and briefly, I would like to make some comments about a possibility of ischemic cardiomyopathy Although this is a known entity, it usually occurs in patients who have had long



Fig 4 Hypertrophied myocardium with interstitial and probable intracellular edema Hematoxylin and eosin stain ×300

standing evidence of angina pectoris or previous myocardial infarctions which our patient did not have He could have however small vessel disease but I doubt it The unsolved question is whether myxedema leads to or accelerates the development of atherosclerosis

In a study by Willius and Haines[10] of 162 patients with severe myxedema 91 per cent had no subjective symptoms of organic cardiovascular disease and a large proportion of their patients were in the fourth fifth and sixth decades of life the age group where the incidence of ischemic heart disease should be higher Andrus[11] has reported that Bartel and Bell found an incidence of 25 per cent of coronary artery disease in a spontaneous myxedema The increase in or the development of angina pectoris is common however during the course of therapy of myxedema. In those patients who have a significant degree of coronary arteriosclerosis the administration of thyroid replacement could be lethal[12]

Our patient died rather soon after the initiation of synthetic thyroid therapy A ventricular arrhythmia and exacerbation of congestive heart failure developed. This could suggest the presence of moderately severe and asymptomatic coronary artery disease However I do feel that this was not a manifestation of ischemic cardiomyopathy but the lethal result of thyroid replacement in a patient with myxedema heart, manifested by an extremely severe degree of myocardial involvement, who may happen to have associated coronary artery disease If that were the case with this patient, probably an important conclusion would be that in the future patients with severe myxedema who are to be given thyroid therapy should have coronary arteriographic studies whether symptomatic or not, from that point of view to determine the extent and degree of disease in the coronary arterial system This could provide valuable information as to the potential risk of this mode of therapy in this type of disease

Autopsy results

At autopsy there was generalized edema and the skin had a rather coarse and rough texture with brownish pigmentation over the forearms and lower legs. There were 2 000 c c of ascitic approximately 1 500 c c of pleural and 200 c c. of pericardial fluid. The heart was hypertrophied, flabby and somewhat globular The chambers were dilated. It weighed 1 000 grams. The ventricular walls measured in average thickness 2 2 cm on the left and 0 5 cm on the right The *myocardium* was of normal color but an ill defined, grayish white infarct measuring 1 5 cm. *in width* extended from the base to mid level in the posterior wall of the left heart. The circumference of the tricuspid valve was 15 cm and that



Fig 5 Chronic nonsuppurative thyroiditis. Hematoxylin and eosin stain ×100

of the mitral valve 12 cm The valves were not deformed The endocardium of the left atrium was irregular with a crescent shaped scar opposite the orifices of the right pulmonary veins However the veins were not narrowed The endocardium of the anterior wall of the left atrium was thick and brown Only a few small foci of endocardial fibrosis were seen in the left ventricle Although focal coronary atherosclerosis was present, the left circumflex and anterior descending branches were widely patent The right coronary artery was as large as the left and at its origin was widely patent. However, a 3 mm segment was almost completely occluded by white fibrous material at the right margin of the heart. From this point onward the lumen widened to a diameter of 1 to 2 mm The vessel formed a widely patent posterior descending coronary artery

The microscopic examination of the coronary arteries showed an 80 per cent occlusion of the right coronary artery by an atheromatous plaque The other arteries did have fibrous and atheromatous plaques but their lumina retained at least 70 to 90 per cent of their patency The small myocardial arteries and arterioles were normal The myocardial fibers were large and had large, square nuclei There were scattered intracytoplasmic vacuoles Sudan IV fat stain alcian blue PAS, and trichrome stains were not helpful in defining the nature of the material in the vacuoles The muscle cells were widely separated from each other most likely due to interstitial edema It is possible that the cytoplasmic vacuoles also represented edema There was no interstitial or perivascular fibrosis, but an old scar was present in the posterior left ventricular wall Fibroelastosis was noted focally in the left ventricle and some areas resembled old organized mural thrombi, although there was no evidence of organizing or acute thrombi Fibroelastosis was also noted in sections of the left atrium

The right lung weighed 1,050 grams and the left lung 760 grams There was focal pleural fibrosis and the lungs were subcrepitant and wet. In the lower lobes there were ill defined areas of consolidation Microscopic examination of the upper lobes showed interstitial fibrosis with aggregates of numerous hemosiderin containing macrophages, dilation of lymphatic channels and dilation and some sclerosis of small veins in the intralobular septa Dilation with some hypertrophy and scarring of the walls of small arteries was also present Large arteries contained atheromatous plaques but there was no vasculitis In the lower lobes there were healing infarcts with several areas of necrosis and reactive interstitial fibrosis with lining cell proliferation in the adjacent parenchyma There were also large, hyalinized scars probably representing healed infarcts In one such area there was an



Fig 6 Upper lung field with interstitial fibrosis Weigert s stain ×40

obliterated artery and there were other arteries with proliferative end arteritic changes marked by narrowing the lumina There were also small arteries containing multichanneled lumina suggesting that this entire pathologic process was due to chronic embolization and repair of infarcts However there were no healing or acute emboli Conspicuous capillary telangiectasis in these areas suggested possibility of an A V shunt although none was demonstrated.

The liver was enlarged (2 280 grams) with changes due to chronic passive congestion Small scars representing usually obliterated central veins were present The etiology of the latter change is not clear since there was no history of excessive alcoholic consumption The spleen was also congested (420 grams) and contained a healed infarct.

The pancreas showed interstitial fibrosis with chronic inflammation fibrosis in adjacent fat, and several hyalinized islets These changes represent chronic pancreatitis. Although there is no history of alcoholic abuse in view of these as well as the hepatic changes, one may wonder about the veracity of the patient s history

The adrenals were rather small (total weight, 6 grams) However the cells of the zona fasciculata did not appear to be lipid depleted, as can be seen after episodes of stress Small nests of mono nuclear inflammatory cells were present throughout the zona reticularis The significance of adrenal size is not clear since the pituitary gland was normal An adjacent autonomic ganglion had proliferative changes characteristic of neurofibromatosis

Old infarcts were found in the kidneys

The thyroid gland weighed 8 grams It was grayish brown in color and very firm It was not adherent to surrounding structures Microscopic examination showed wide bands of collagen surrounding nodules of degenerated acini with very little colloid, scattered, multinucleated giant cells and abundant chronic inflammatory infiltrate There was no lymphoid follicle formation There were a few large acini with colloid and the histologic pattern was that of chronic nonsuppurative (giant cell) thyroiditis

Although grossly the skin was described as myxedematous representative sections did not show a dermal infiltrate or keratotic plugging of hair follicles Only a few sweat ducts were dilated and filled with keratin like material.

In summary there was a severe destructive chronic thyroiditis with equivocal histologic evidence of myxedema in the skin to support clinical evidence of hypothyroidism There was an edematous markedly hypertrophied, and dilated heart In myxedema the clinically suspected marked enlargement of the heart is often due to massive pericardial effusion but not in this case The massive cardiac enlargement could not be explained on the basis of atherosclerotic coro



Fig 7 Lower lung field with scar and an occluded elastic pulmonary artery Weigert s stain ×40

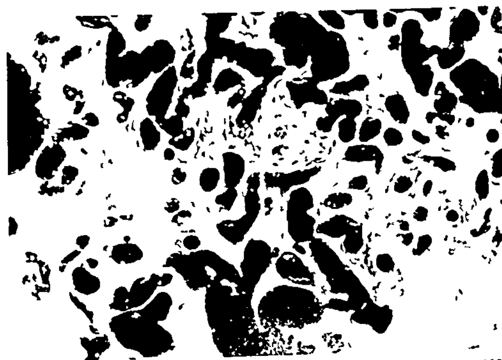


Fig 8 Lower lung field with hemangiectasis in scarred area Trichrome stain ×100

nary artery disease The atherosclerosis was not as severe as one might expect in hypothyroidism[13,15] and there was only one small scar in the wall of the left ventricle posteriorly There also was no histologic evidence of disease in small intramural arteries and arterioles of the myocardium Although there was histologic evidence of interstitial and intracellular edema of the myocardium, the cardiac enlargement was due principally to muscle hypertrophy Special stains did not demonstrate an interstitial accumulation of mucoproteins, as is common in myxedema[13,14] Although cardiac hypertrophy is described in myxedema there is no convincing evidence that true myocardial hypertrophy in myxedema occurs without some other contributing disease Idiopathic cardiomyopathy is at times invoked to account for cardiac hypertrophy in some patients Cardiomyopathy frequently is characterized by paucity of histologic changes in a large

and dilated heart. This possibility of course exists in this patient. As Dr Susmano mentioned, there was no history of viral infection or alcohol intake However presence of chronic pancreatitis and hepatic scars reminiscent of so called central hyaline sclerosis certainly might suggest the latter etiology

The interstitial pulmonary fibrosis may be due in part, to prolonged congestive heart failure or some other unknown factor The lower lobes of the lungs had occluded and partly occluded pulmonary arteries most likely due to recurring emboli with healing infarcts and scars representing healed infarcts It is well known that showers of small emboli usually originating from mural intracardiac thrombi tend to recur and can eventually lead to pulmonary hypertension This is particularly true in patients with cardiac failure characterized by chamber dilation [16] A peculiar vascular capillary ectasia in these areas suggested a possible A V (bronchopulmonary artery collateral) anastomosis, thus further decreasing the arterial oxygenation The most severe involvement was in the lower lobes in keeping with the known predilection of pulmonary emboli to localize and produce infarcts in the lower lobes The pulmonary vascular lesions represented an old process, however apparently clinically the possibility of pulmonary hypertension induced by chronic embolization was not suspected. Furthermore the clinically demonstrated hypothyroidism of course could have contributed to the cardiac burden Therefore there are at least two mechanisms, whether a primary myocardial disease or the so called myxedema heart as well as pulmonary vascular impairment secondary to chronic embolization that could account for the progressive and severe congestive heart failure

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Noninvasive preoperative diagnosis of cor triatriatum with ultrasonocardiotomogram and conventional echocardiogram*

Yasuharu Nimura, M D M Sc**
Masayuki Matsumoto M D**
Shintaro Beppu, M D**
Hirohide Matsuo M D***
Hiroshi Sakakibara M D**
Hiroshi Abe M D**
Osaka Japan

The echocardiogram is now routinely used in cardiology because it has a great advantage of noninvasive visualization of the intracardiac structures without giving discomfort to the examinee However, because the heart moves during ultrasonic scanning, the application of the two dimensional ultrasonotomogram[1,2] to the heart has been difficult [3] To overcome this difficulty efforts have been made by Kikuchi and co workers [4-6] Omoto [7] and Åsberg [8] Kikuchi introduced with satisfactory results the method in which the unblanking time of the cathode ray tube was controlled by an electronic circuit Lately Bom and co workers [9] King and co workers [10,11] Gramiak [12] and Eggleton[13] are beginning to use a newer technique The ultrasonocardiotomogram seems to offer a useful aid for the visualization of the intracardiac structure, for the analysis of heart motion and for the detection of intracardiac abnormalities [5,14-17]

Cor triatriatum[18-31] is a type of congenital malformation in which an abnormal fibromuscular septum exists across the left atrial sphere, dividing the latter into the upper and lower chambers As cor triatriatum resembles mitral stenosis in its hemodynamic conditions preoperative examination techniques to differentiate the two diseases are needed In the present study, an attempt was made to give a preoperative diagnosis of cor triatriatum by means of the ultrasonocardiotomogram on the basis of the principle introduced by Ebina and co workers [4]

Materials

Two cases of cor triatriatum were examined using the ultrasonocardiotomogram and the conventional echocardiogram

The first case was a 14 year old school boy, H A who had been diagnosed in a few hospitals as having mitral stenosis He was referred to Osaka University Hospital for ultrasound examination

The physical examination revealed a late diastolic rumbling murmur of Grade II by Levine near the left parasternal line in the fourth interspace The right anterior oblique chest roentgenogram revealed a left atrial enlargement at a slightly higher position than that usually seen in mitral stenosis The electrocardiogram suggested a right ventricular hypertrophy and a left atrial overloading Studies on pressure revealed a mean pulmonary artery pressure up to 34 mm Hg and a pulmonary capillary wedge pressure up to 25 mm Hg Ultrasound examinations were made subsequently with the results which are to be discussed later Further examinations were performed In the

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The First Department of Medicine Osaka University Medical School Fukushima ku Osaka 553 Japan and the Central Laboratory for Clinical Investigation Osaka University Hospital Fukushima ku Osaka 553 Japan

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Reprint requests to Dr Yasuharu Nimura The First Department of Medicine Osaka University Medical School 3 chome Dojima Hamadori Fukushima ku Osaka 553 Japan

angiocardiogram a septum was found in the left atrial area dividing the latter into two parts An opening was observed in an intra atrial septum which connected the two parts

At operation an anomalous septum of 1 mm in thickness was found extending from the right superior rim of the oval fossa to the superior margin of the left auricle The left atrial sphere was divided into two compartments by this intra atrial septum i e the right posterior superior chamber the accessory chamber and the left anterior inferior chamber the left atrium A connecting opening about 8 to 12 mm in diameter was located to the left and posterior to the oval fossa (Fig 1) The surgical findings strongly suggested cor triatriatum of Type I A as reported by Lucas and Schmidt [23]

The second case was a 7 year old girl Y S who had been diagnosed as having congenital heart disease since her neonatal days Studies on pressure revealed a mean pulmonary artery pressure up to 22 mm Hg and a pulmonary capillary wedge pressure up to 17 mm Hg At operation an abnormal septum was confirmed in the left atrial area with a diagnosis of cor triatriatum

Before describing the specific nature of the ultrasound findings in cor triatriatum a brief communication on the tomographic findings of the heart, based on the authors experience with 250 healthy and diseased subjects will be given for comparison

Methods

The equipment used was a commercially available two dimensional ultrasonocardiotomograph (Aloka SSD 10 made by Japan Radiation and Medical Electronics Co) using a 2 25 MHz. 30 mm. diameter transducer with a 20 cm focus and a pulse repetition rate of 937 5 Hz The transducer was operated in a vinyl bag filled with bubbleless water which was placed on the chest wall of the patient who was being examined in the supine position (Fig 2) The distance of the transducer from the chest wall was set at over 10 cm so that the ultrasound beam was focused at a conjectured depth of the midportion of the heart. The unblanking time of a cathode ray tube was about 50 msec in duration It could be set at any phase in the cardiac period with a gate circuit being triggered by the R wave in the electrocardiogram Sector scan was used.

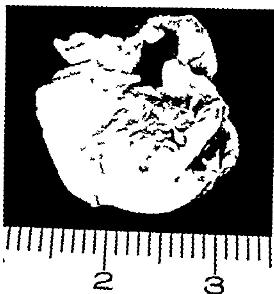
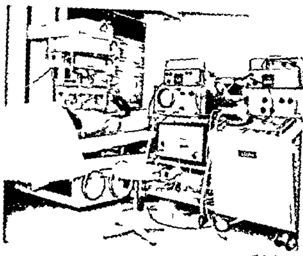


Fig 1 The excised septum the connecting opening is noted. (Through the kindness of Dr H Nishizaki Ohtemae Hospital Department of Surgery)


Fig 2 Equipment used in the present study

For the second case another type of ultrasonocardiotomograph (Aloka SSD 30B made by the same company) was used, utilizing a 2 25 MHz. disc shaped transducer of 10 mm in diameter Contact sector scan was performed.

The conventional echocardiogram was recorded with the same equipment Time sequential recordings of the motion of an intracardiac structure in a direction shown in the tomogram were nothing but the conventional echocardiograms of the above structure The direction of ultrasound beam for the conventional echocardiogram could be superimposed as

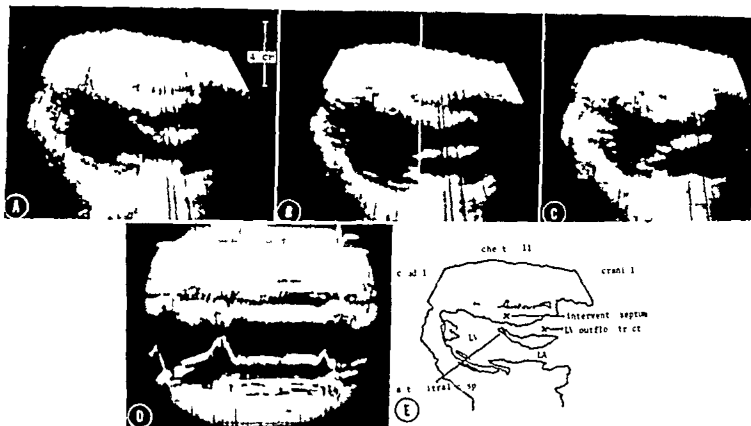


Fig 3 A series of ultrasonocardiotomograms of a healthy subject along the long axis of the heart, viewed from the left *A* At early diastole The interventricular septum the left ventricle the mitral leaflets and the left atrium are recorded. They are illustrated in the schema The mitral valve is recorded at its maximum opening *B*, At mid diastole The mitral valve is in its semi closed position *C*, At late systole the mitral valve is closed *D* A conventional echocardiogram of the mitral valve of the same subject This was recorded with an ultrasound beam shown as a white line in the tomogram (*B*) The tomogram (*B*) reveals that the ultrasound beam penetrates the mitral valve *E* A schema of the tomogram (*A*) (T K a 22 year-old man)

a white line on the tomogram, so the geometrical relations between the beam direction for the conventional echocardiogram and intracardiac structures in the tomogram were easily understood

Results

General description on the tomographic findings of the heart Interpretation of the ultrasonocardiotomogram is generally easy regarding a section along the long axis of the heart, a sagittal section at the left sternal border and a transverse section in the left third or fourth intercostal space

A section along the long axis of the heart usually involves the left atrium, the mitral valve the left ventricle, the aortic root and the interventricular septum (Fig 3) The right ventricle presents only a narrow area in healthy subjects, but shows a broad area in cases with right ventricular enlargement The transparent area behind the mitral valve is the left atrium The part near the mitral ostium of the posterior wall of the left atrium exhibits a slight rise in diastole which continues caudally to the mitral posterior leaflet It is possible to recognize the position of the mitral valve at any phase in a cardiac period (Fig 3)

In a sagittal section near the left sternal border, there is an oblique cut of the structure from the aortic root to the mitral valve (Fig 4)

In a transverse section at a level of the third or fourth intercostal space, the interventricular septum the outflow of the left ventricle the root of the mitral valve, and the left atrium are involved, but only partly involved as the sternum and the lungs shut off the ultrasound beam (Fig 5) In cases with right heart enlargement especially in children however, an entire transverse section of the heart can be recorded (Fig 6)

Cor triatriatum In the case of H A, the rate of diastolic descent of the echo curve of the anterior mitral leaflet was 74 mm per second in the con

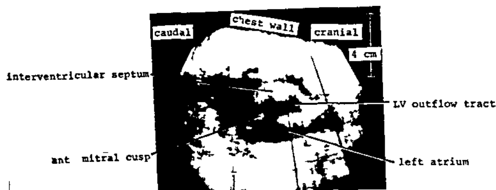


Fig 4 A sagittal ultrasonocardiotomogram near the left sternal border at mid diastole viewed from the left. The outflow tract of the left ventricle and the left atrium behind it are revealed. The interventricular septum is not recorded as a continuous echo since it crosses the section plan obliquely (T K a 22 year-old man)

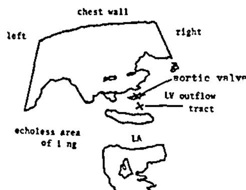




Fig 5 A transverse ultrasonocardiotomogram in the third intercostal space at late diastole viewed from the cranial side The outflow tract of the left ventricle with the aortic valve and the left atrium are recorded. There are echoless areas due to the sternum and the lung in the right and left sides of the heart echoes respectively (S N a 29 year-old man)

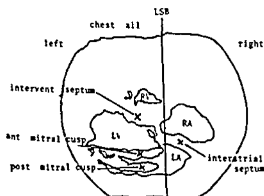




Fig 6 A transverse tomogram in the fourth intercostal space at late diastole, viewed from the cranial side The interventricular septum, the interatrial septum, the mitral leaflets and the four chambers of the heart are clearly recorded (S. M., a 6-year-old girl, after surgery for atrial septal defect)

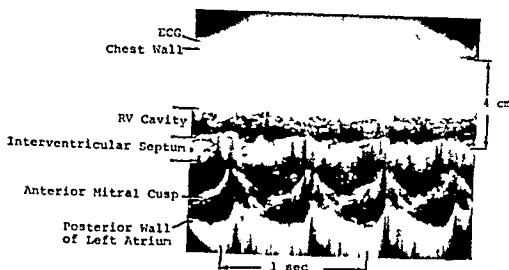


Fig 7 The echo curves of the anterior mitral leaflet and of the posterior wall of the left atrial area of the first case Because of tachycardia the presystolic peak of the anterior mitral echo curve is fused into the preceding early diastolic peak This echocardiogram was recorded by a beam in the direction shown as a white line (*A*) in Fig 9

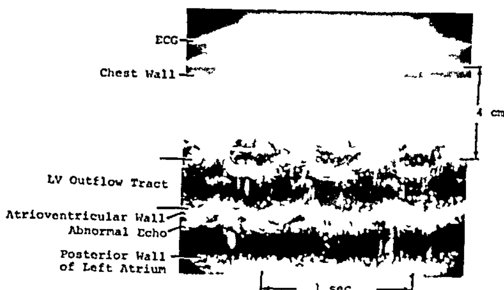


Fig 8 An echocardiogram near the aortic root of the first case An unusual linear echo (→) is observed just behind the atrioventricular wall This echocardiogram was recorded by a beam in the direction shown as a white line (*B*) in Fig 9

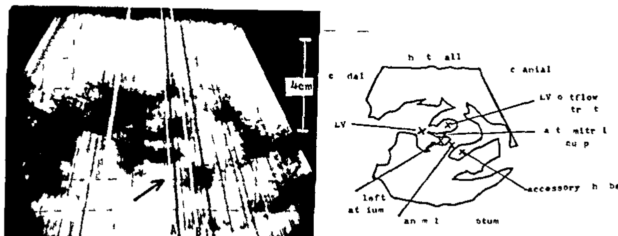


Fig 9 An ultrasonocardiotomogram of the first case A sagittal section near the left sternal border at late diastole viewed from the left A process like anomalous echo (↗) is observed showing a division of the left atrial area into two parts



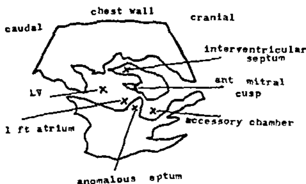


Fig 10 An ultrasonocardiotomogram along the long axis of the heart in diastole viewed from the left A process like anomalous echo (/) is observed.



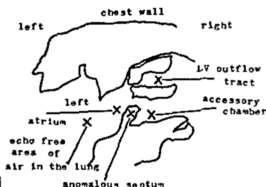


Fig 11 A transverse section in the third intercostal space in diastole, viewed from the cranial side In the left atrial area an anomalous echo (/) is observed from left posterior to right anterior

ventional echocardiogram (Fig 7) An uncommon rise was noted in the echo of the posterior wall of the left atrial area from late diastole to the following mid systole In the echocardiogram of the base of the heart there was noted an uncommon echo curve just behind the aortic root (Fig 8)

In two ultrasonocardiotomograms in a sagittal section viewed from the left near the left sternal border (Fig 9) and in a section along the long axis of the heart (Fig 10) a process like echo was noted stretching anterocranially from the posterior wall of the left atrial area This echo divided the left atrial area into two parts anterocaudal and posterocranial

In a transverse section viewed from the cranial side at a level of the lower part of the third intercostal space (Fig 11) an uncommon echo was noted running through in a direction from right anterior to left posterior in the left atrial area

The above findings led to the interpretation that there was a diaphragm like structure in the left atrial sphere dividing the latter into the left anterior caudal and the right posterior cranial compartments i e the left atrium and the accessory chamber

Postoperatively the above echo was no longer found in a section (Fig 12) recorded under almost the same anatomic conditions as those in Fig 9 In the conventional echocardiogram performed postoperatively there remained a slight rise in the posterior wall of the atrial area (Fig 13)

The second case also revealed an abnormal echo obliquely across the left atrial area (Fig 14) In the conventional echocardiogram a broad echo band was noted in the left atrial area behind the aortic root (Fig 15) Its site in the left

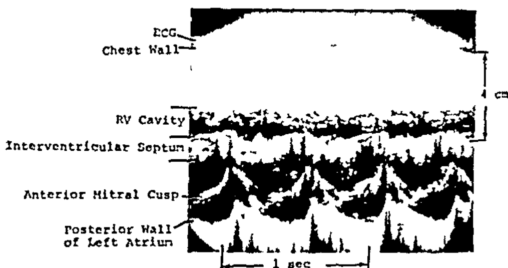


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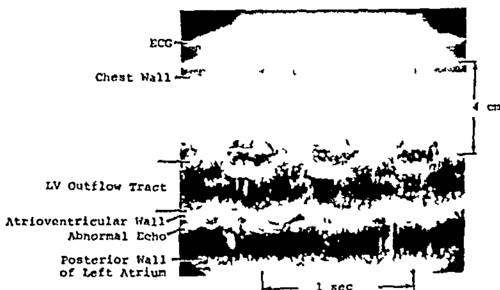
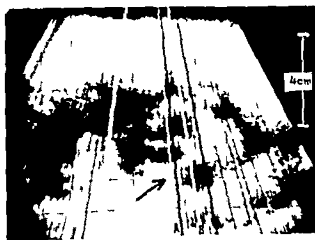


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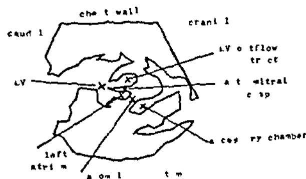


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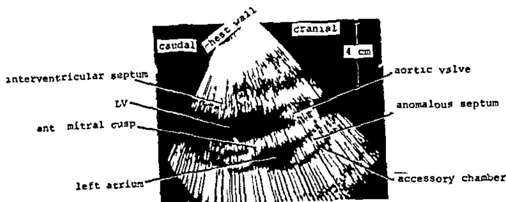


Fig 14 A tomographic section along the long axis of the heart at mid-diastole of the second case viewed from the left An anomalous echo which exists obliquely across the left atrial area is observed.

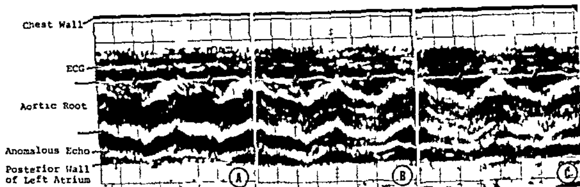


Fig 15 A series of the conventional echocardiograms obtained in the second case *A* An anomalous echo curve is observed in the left atrial area behind the outflow tract of the left ventricle *B*, The direction of the ultrasound beam was slightly changed from that used for the echocardiogram (*A*) The anomalous echo curve in the left atrial area can be found in a slightly higher position than in the echocardiogram (*A*) *C*, After moving the beam more cranially the anomalous echo curve was recorded just behind the posterior wall of the aortic root

corresponded, referring to the anomalous echo in the tomogram to a part near the posterior wall of the left atrial area and to the tip of the anomalous echo respectively If the echocardiogram in a direction penetrating the middle of the anomalous echo in the tomogram had been taken the anomalous echo would have appeared as a broad band in the middle of the left atrial area. But, there was no chance to record such an echocardiogram in the first case As is seen by the following however this consideration was confirmed by the findings in the second case

The location of the origin of the anomalous echo concerned which was assumed from the above results, coincided fairly well with the location of the anomalous septum in the left atrial sphere which was confirmed in surgery Thus it was concluded that the process like echoes in the tomograms (Figs. 9 and 10) were considered to represent a section of the anomalous septum in the left atrial sphere The faintness of this process like echo in its tip seemed to represent the opening

Based on the above mentioned results ultrasound examinations were performed on the second case which had initially been diagnosed as cor triatriatum by angiocardiogram Conclusively a broad band echo in the left atrial area was observed in the conventional echocardiogram As expected from the findings of the first case and the tomogram of the second case the site of this abnormal broad band in the left atrial area changed from the vicinity of the posterior wall of the left atrial area to that of the aortic root as the direction of the ultrasound beam was changed cranially

Cor triatriatum has, by routine examination a similarity to mitral stenosis in its clinical data

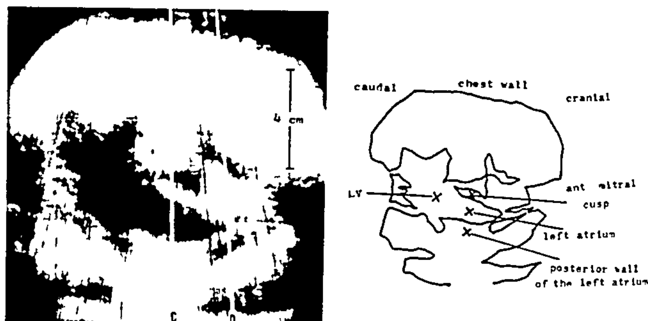


Fig 12 A postoperative ultrasonocardiotomogram at nearly the same position as in Fig 9 at late diastole

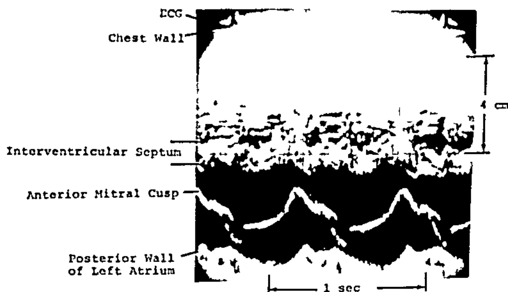


Fig 13 A postoperative echocardiogram of the anterior mitral leaflet and of the posterior wall of the left atrial area This echocardiogram was obtained by a beam in the direction shown as a white line (*C*) in Fig 12

atrial area became nearer to the aortic root as the direction of ultrasound beam was directed cranially

Discussion

In the first case of cor triatriatum marked abnormalities were found in the left atrial sphere In surgery this case proved to be cor triatriatum of Type I A of Lucas and Schmidt [23]

In the ultrasound cardiogram the caudal half of the posterior wall of the left atrium[32] generally shows an excursion of several millimeters synchronously with the heart beat [33] In the first case however, the movement of the posterior wall of the left atrial area was much larger than usual (Fig 7) An echo which is not commonly seen in healthy subjects was noted just behind the aortic root (Fig 8) Following this a two dimensional ultrasonocardiotomography was performed whereby an uncommon process like echo was obtained which divided the left atrial area into two parts

The conventional echocardiograms in the first case shown in Figs 7 and 8, were recorded with ultrasound beams in the direction of white lines A and B, respectively in the tomogram of Fig 9 These lines showed that the uncommon echoes in the conventional echocardiograms (Figs 7 and 8)

4 Intra atrial echoes which must be differentiated from the echoes of an anomalous septum in cor triatriatum were also discussed.

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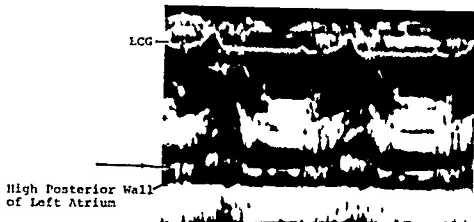


Fig 16 A linear echo (→) in the left atrium in a healthy subject. To record this echo the ultrasound beam should be directed a little laterally and cranially from the aortic (T H a 28 year-old man)

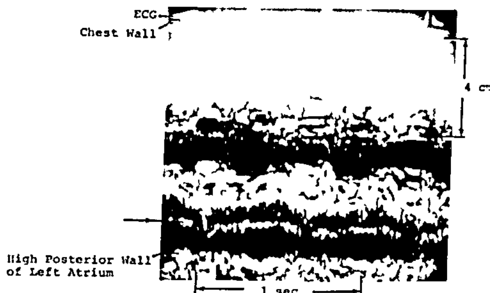


Fig 17 The same kind of intra atrial echo (→) as in Fig 16 was also observed in the present first case postoperatively This picture was recorded by a beam in the direction shown as a white line (*D*) in Fig 12

As a matter of fact, the first case had been diagnosed as mitral stenosis in other hospitals The results of the ultrasound examination in the present cases suggest that the ultrasound examination is a useful noninvasive method for a preoperative diagnosis of cor triatriatum Recently, Lundstrom[24] also reported an abnormal echo which showed a complicated motion in the left atrial area in a case of cor triatriatum

Anomalous echoes of intra atrial tumors[34 37] and of intra atrial thrombi[38 39] in the left atrium are already reported The echoes are flocculent and layered ones, so that the echo of the anomalous septum in cor triatriatum may be differentiated from the abovementioned intra atrial echoes Even in healthy subjects however, if the ultrasound beam is directed somewhat laterally and cranially from the aortic root a thin linear echo curve almost parallel to the aortic root is often observed in the upper part of the left atrium (Figs 16 and 17) On the basis of anatomy and findings in the ultrasonocardiotomogram, it is presumed that this echo is related to the opening of the left pulmonary vein This echo must be carefully differentiated from the intra atrial anomalous echo of cor triatriatum

Summary

1 A preoperative diagnosis of cor triatriatum was studied with ultrasound techniques

2 The echo from an anomalous septum was found in the left atrial area in a conventional echocardiogram and in two dimensional ultrasonocardiotomograms

3 The present data seemed to shed light in establishing a preoperative diagnosis as well as a differential diagnosis of cor triatriatum from mitral stenosis

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Acute respiratory insufficiency and cor pulmonale

Pathophysiology clinical features and management Part II Management

Robert J Malovany M D *
Spencer K Koerner M D **
Bronx, N Y

The mortality associated with an episode of acute respiratory insufficiency was formerly in the range of 30 to 50 per cent clearly an unacceptable figure Furthermore the highest mortality occurred in patients requiring tracheostomy a frequent development in the course of patients with chronic obstructive pulmonary disease (COPD) The ensuing discussion will deal with some of the newer approaches to management of ventilatory failure in these cases.

Oxygen Upon admission to the hospital the PaO_2 of these patients is frequently in the 20 to 40 mm. Hg range with an elevated $PaCO_2$ which is rarely above 80 mm Hg Whereas in the past, patients with central nervous system (CNS) disturbance and severe degrees of hypercapnea and hypoxia were immediately intubated it seems that hypoxia may play a larger role in their symptoms and their mental status may be only minimally impaired by high levels of CO_2 if acidosis is not marked. In such a case correction of severe hypoxia with controlled oxygen via a Ventimask can usually be accomplished without resorting to mechanical ventilation [12] Although the $PaCO_2$ may rise somewhat with oxygen administration these patients usually have elevated bicarbonate levels and are sufficiently buffered so that radical changes in pH do not occur Only when the PaO_2 is allowed to exceed the threshold of the carotid body chemoreceptors will CO_2 narcosis develop The upper limit of PaO_2 desired will, therefore be approximately 60 mm. Hg Arterial oxygen tensions of 50 to 55 mg will result in O_2 saturations of about 80 to 85 per cent which in most cases barring severe anemia will be sufficient to maintain aerobic metabolism This therapeutic method has been advocated by Campbell[12] who feels that intubation and mechanical ventilation should be reserved for those patients who become unrousable and unable to clear their secretions

Ventimasks allow for the constant delivery of an FIO_2 of 0 24 0 28 0 35 or 0 40 and one can predict the resultant PaO_2 according to Mithoeffer Keighley Karetzky[13] with the administration of any of these mixtures as long as the initial PaO_2 is known

Antibiotics Since pulmonary infection may frequently play a role in acute exacerbation of chronic lung disease antibiotics are almost always indicated Sputum smear and culture should be obtained on admission in search of a specific etiologic agent, however a mixed flora is frequently found. The organisms most commonly associated with acute infections in chronic bronchitis are *Diplococcus pneumoniae* and *Hemophilus influenzae* so that, in the absence of an identifiable cause ampicillin or tetracycline should be given since their spectrum includes the common organisms.

Special attention has to be given to clearance of bronchial secretions. In addition to infected material which has to be drained the sputum increases airway resistance thereby increasing the work of breathing and worsening ventilation perfusion relationships. These processes must be

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Reprint requests to Dr Spence K Koerner Mo tefiore Hospital and Medical Center 111 E 210th St., Bronx N Y 10467

*F llow D ision of Pulmonary Med ine, Montefiore Hosp tal and Medical Cente

**Chief Di ision of Pulmonary Medicine Montefiore Hospital and Medic l Center and Assistant Professor of Medicine Albert Einstein College of Medic e.

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Repri t requests to Dr Spe cer K. Koerner Montefiore Hosp tal and Medical Ce ter 111 E. 210th St Bronx N Y 10467

*Fellow D ision f Pulmonary Med cine, Montefi re Hosp tal and Medical Ce ter

**Chief, Di ision of Pulmonary Medicine M tefiore Hosp tal and Medical Center and Assista t *Professor of Medicine* Albert E nstein College of Medicine

reversed by encouraging the patient to cough and/or by nasotracheal suction This is a particularly important factor if mental obtundation begins to occur since suctioning as often as every 15 minutes may improve ventilation sufficiently to obviate the necessity of intubation and mechanical ventilation

Intermittent positive pressure breathing (IPPB) The use of IPPB has been advocated in the acute management of patients in respiratory failure especially in those with bronchitis or bronchospasm The proposed advantages include reduction in work of breathing, overcoming airway resistance, administration of bronchodilators and improved alveolar ventilation The short term and long term studies of the effects of IPPB have not shown a clear cut beneficial effect. Immediate effects are similar to those effects seen with voluntary hyperventilation and prolonged use of IPPB treatments has not resulted in improved pulmonary function IPPB is an effective means of administering bronchodilators but perhaps no better than hand nebulizers for this purpose It is certainly of no value to a patient too obtunded or confused to use it properly Sukumalchantra, Park, and Williams[14] have warned that although IPPB may increase total ventilation, much of this will go to areas which are already overventilated which will result in an excessive increase in physiologic dead space The end result is an increase in minute ventilation without an increase in alveolar ventilation IPPB might, therefore increase rather than decrease the work of breathing, especially if the patient is not relaxed. A decrease in cardiac output resulting from high intrathoracic pressures and decreased venous return may occur Pneumothorax has also been implicated as a complication of IPPB as well as pulmonary infection secondary to contamination of the apparatus In spite of these limitations, many patients seem to be benefited by IPPB Perhaps this is because of the active involvement of trained therapists working with the patient, offering encouragement and constantly re evaluating the clinical situation

Bronchodilators and steroids Many patients with COPD admitted in respiratory failure show evidence of bronchospasm and increased bronchial inflammation as evidenced by increased cough sputum production, and wheezing Bronchodilators have shown great usefulness in these patients by reducing airway resistance and thus reducing work of breathing Isuprel administered by IPPB or hand nebulizer is often useful as is intravenous aminophyllin.

A few patients with bronchospasm and severe bronchial inflammation fail to respond to bronchodilators In these patients a short course of parenteral corticosteroids may be effective as a bronchodilator and in reducing bronchial edema and bronchial secretions There are potential risks of steroid therapy which must be weighed against the possible benefits and their use should not be prolonged in COPD unless a bronchospastic component is present which is refractory to other therapeutic modalities

Intubation and mechanical ventilation Throughout the early phases of the hospitalization of a patient with respiratory insufficiency the major decision to be made revolves around the necessity for intubation While the absolute level of P_{CO_2} was frequently the deciding factor in the past, it is currently felt that the mental status of the patient is more important As long as the patient is relatively alert and capable of clearing secretions it is usually not necessary to institute mechanical ventilation regardless of the Pa_{CO_2} This approach has been one of the major factors in the marked reduction of mortality in the treatment of acute ventilatory failure The recognition that correction of anoxia and attention to proper bronchial toilet could be accomplished without instrumentation now enables the patient to regain his usual status gradually without unnecessary intubation or tracheostomy

Of course such a method would be a total failure without the nursing and medical staff necessary to insure the proper monitoring of the patient An intensive care unit preferably a pulmonary ICU is a virtual necessity for the frequent evaluation of the patient s mental and physical status nasotracheal suctioning, administration of IPPB etc

If mental obtundation develops or adequate bronchial toilet cannot be maintained, endotracheal intubation should be performed preferably with a tube which contains a high compliance cuff to lessen the likelihood of tracheal damage After a period of mechanical ventilation with correction of blood gases, an attempt at weaning should be made Although endotracheal tubes can be kept in place for as long as two weeks it is our recommendation to at

tempt extubation within five days. A detailed description of weaning is beyond the scope of this discussion but the patient should be allowed progressively longer periods off the respirator with an appropriate humidified oxygen mixture administered via a T piece attached to the endotracheal tube. Intermittent mandatory voluntary ventilation (IMVV) has recently been proposed as a method of alternating progressively increasing periods of spontaneous ventilation and decreasing mechanical ventilation[15] If the patient cannot be extubated within five days tracheostomy should be performed. Following this the weaning process can be performed much more gradually.

When patients are artificially ventilated they are subject to respirator associated complications (1) Continuous ventilation at constant tidal volumes will result in areas of microatelectasis which result in an increased venous admixture because of their low VA/Q. This can be prevented by frequent hyperinflation of the lungs by either a sigh addition on the ventilator or manually with an Ambu bag. (2) Prolonged exposure to high inspired oxygen tensions will lead to pulmonary oxygen toxicity so it is important to ventilate patients with the lowest FIO_2 consistent with the desired PaO_2. (3) Since the work of breathing has been almost eliminated when patients are mechanically ventilated, it is sometimes easy to lower $PaCO_2$ to normal or normal levels quite rapidly. This can result in severe alkalosis in patients with a compensatory increase in bicarbonate. It is important, therefore to carefully monitor arterial pH as well as O_2 and CO_2, and to allow the kidneys to eliminate excess bicarbonate over a period of several days. (4) With an airway in place the patient cannot cough so frequent suctioning of secretions is essential to prevent atelectasis and worsening of VA/Q relationships. Strict attention must be paid to sterile technique while suctioning. (5) Mucosal lesions of the trachea have been the result of pressure necrosis from cuffed endotracheal and tracheostomy tubes. High compliance cuffs are now available which inflate with large volumes of air but with pressures low enough that blood flow to the tracheal mucosa is not occluded. These cuffs should result in the elimination of tracheal stenosis and tracheomalacia as complications of intubation[16]

Treatment of heart failure. As cor pulmonale and heart failure in respiratory failure are secondary to hypoxemia and hypercapnea reversal of these factors is the best means of improving cardiac function.

Digitalis. The efficacy of digitalis in the treatment of right heart failure has been controversial for many years. Studies of pulmonary hemodynamics following administration of digitalis have yielded variable results ranging from a decrease to an increase in right ventricular output or no change at all.[17,18] In some cases where improvement occurred, it is possible that undetected left ventricular failure was present and the benefits derived from digitalis were in reality a reflection of improved left heart function. This is probably not the case in the patients with cor pulmonale and right heart failure studied by Jezek and Schrijen[19] They had improved cardiac function after receiving Cedilanid although the pulmonary artery wedge pressure was not elevated initially. Since digitalis toxicity is a serious danger in the management of respiratory failure because of hypoxia, acidosis and electrolyte abnormalities, it should be used with caution and only when definitely indicated. The indications at this point in time are probably limited to certain supraventricular arrhythmias and when there is evidence of left ventricular failure.

Diuretics. Diuretics have shown definite effectiveness in reducing peripheral edema and also in reducing the circulatory load on the right heart. Noble and co workers[10] have shown in addition actual improvement in blood gases after treatment with furosemide. Perhaps elevated peripheral venous tone may induce central distribution of excess fluid. Elevated bronchial venous pressures may also contribute to excess lung water. The excess fluid would further aggravate gas exchange and respiratory mechanics and diuretics would thus be effective in improving pulmonary function.

Respiratory stimulants. Respiratory stimulants have been suggested as a means of increasing central respiratory drive in respiratory failure. In theory stimulants would help maintain reasonable levels of $PaCO_2$ while allowing greater concentrations of oxygen to be administered. Intubation and assisted ventilation would thus be avoided giving clinicians time necessary to institute therapy and reverse possible precipitating factors. Many stimulants advocated in the past

have narrow toxic to therapeutic dose ratios and therefore had many side effects Moser and co workers[20] administered doxapram to 78 patients in respiratory failure In a two hour period, oxy gen therapy resulted in excessive CO_2 retention in 36 8 per cent of the patients receiving placebo but in only 17 5 per cent of those receiving dox apram However in spite of this short term ad vantage 40 per cent of both groups later re quired intubation leaving its efficacy in doubt

Enthusiasm for respiratory stimulants is not widespread. While they have been shown to in crease ventilation this increase may be at the ex pense of increased oxygen consumed by re spiratory muscles Patients in respiratory failure are already trying to overcome high airway resis tance and/or decreased lung and chest wall compliance Stimulants do nothing to overcome these mechanical factors, they only drive already overtaxed respiratory muscles The benefits of in creased ventilation may, in the long run, be nullified by increased oxygen consumed by re spiratory muscles.

Monitoring Monitoring of various parameters is important for evaluation of the patients' con dition and the effects of therapy Electrocar diogram monitoring is necessary in view of the high incidence of arrhythmias in these patients Tidal volume and minute ventilation are easily measured during mechanical ventilation and can be obtained intermittently with a spirometer on spontaneously breathing patients Monitoring of arterial blood gases and clinical status are the best parameters of adequacy of alveolar ventila tion Elaborate systems for continuous monitor ing of blood or arterial gases are available which are helpful in deriving research data but are not crucial to the management of these patients. The development of flow directed balloon tipped catheters which can be inserted without requir ing fluoroscopy has made the measurement of pulmonary wedge pressure feasible in the ICU This is helpful in assessing the role of left ventricular failure in respiratory decompensa tion

It cannot be emphasized enough however that there is no substitute for careful clinical evalua tion and that the numbers obtained by the various pieces of monitoring apparatus are only adjuncts to the clinical impression

The mortality of patients admitted in respiratory failure has declined considerably in recent years Pontopidan Geffin and Lowen stein[21] quote their experience at the Respiratory Unit of the Massachusetts General Hospital showing a mortality of 35 to 40 per cent in the years 1961 through 1965 Since 1965 the mor tality rate has dropped to 10 to 20 per cent Rogers Weiler, and Ruppenthal[22] at the Hospital of the University of Pennsylvania report a simi lar experience with a 55 per cent mortality rate for patients with COPD admitted to the general wards and treated with mechanical ventilation in the years 1965 to 1968 Subsequent to this period, all patients with ventilatory failure were admitted to the respiratory intensive care unit with a dramatic reduction in mortality to 19 per cent in those patients requiring mechanical ven tilation and an overall mortality of 12 per cent for all patients admitted with COPD and respiratory insufficiency

Although all the therapeutic modalities dis cussed are of importance, the development of respiratory intensive care units staffed by well trained personnel along with the conservative approach to therapy, based on controlled oxygen therapy, appear to be the major factors in the marked reduction in mortality of patients with respiratory insufficiency

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have narrow toxic to therapeutic dose ratios and therefore had many side effects Moser and co workers[20] administered doxapram to 78 patients in respiratory failure In a two hour period oxy gen therapy resulted in excessive CO_2 retention in 36 8 per cent of the patients receiving placebo but in only 17 5 per cent of those receiving dox apram However, in spite of this short term ad vantage 40 per cent of both groups later re quired intubation leaving its efficacy in doubt

Enthusiasm for respiratory stimulants is not widespread. While they have been shown to in crease ventilation this increase may be at the ex pense of increased oxygen consumed by re spiratory muscles Patients in respiratory failure are already trying to overcome high airway resis tance and/or decreased lung and chest wall compliance Stimulants do nothing to overcome these mechanical factors, they only drive already overtaxed respiratory muscles The benefits of in creased ventilation may in the long run, be nullified by increased oxygen consumed by re spiratory muscles.

Monitoring Monitoring of various parameters is important for evaluation of the patients con dition and the effects of therapy Electrocar diogram monitoring is necessary in view of the high incidence of arrhythmias in these patients Tidal volume and minute ventilation are easily measured during mechanical ventilation and can be obtained intermittently with a spirometer on spontaneously breathing patients Monitoring of arterial blood gases and clinical status are the best parameters of adequacy of alveolar ventila tion Elaborate systems for continuous monitor ing of blood or arterial gases are available which are helpful in deriving research data but are not crucial to the management of these patients The development of flow directed balloon tipped catheters which can be inserted without requir ing fluoroscopy has made the measurement of pulmonary wedge pressure feasible in the ICU This is helpful in assessing the role of left ventricular failure in respiratory decompensa tion

It cannot be emphasized enough, however that there is no substitute for careful clinical evalua tion and that the numbers obtained by the various pieces of monitoring apparatus are only adjuncts to the clinical impression

The mortality of patients admitted in respiratory failure has declined considerably in recent years Pontopidan, Geffin and Lowen stein[21] quote their experience at the Respiratory Unit of the Massachusetts General Hospital showing a mortality of 35 to 40 per cent in the years 1961 through 1965 Since 1965 the mor tality rate has dropped to 10 to 20 per cent. Rogers, Weiler, and Ruppenthal[22] at the Hospital of the University of Pennsylvania report a simi lar experience, with a 55 per cent mortality rate for patients with COPD admitted to the general wards and treated with mechanical ventilation in the years 1965 to 1968 Subsequent to this period all patients with ventilatory failure were admitted to the respiratory intensive care unit with a dramatic reduction in mortality to 19 per cent in those patients requiring mechanical ven tilation and an overall mortality of 12 per cent for all patients admitted with COPD and respiratory insufficiency

Although all the therapeutic modalities dis cussed are of importance the development of respiratory intensive care units staffed by well trained personnel along with the conservative approach to therapy based on controlled oxygen therapy, appear to be the major factors in the marked reduction in mortality of patients with respiratory insufficiency

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Myocardial infarction after propranolol withdrawal

A number of observers have recently reported the development of acute myocardial infarction in patients with angina pectoris, associated with the abrupt cessation of propranolol therapy [1-3] These observations are to date anecdotal and controlled studies have not been reported. However if the discontinuation of propranolol were responsible for the induction of myocardial damage a role for the drug in the prevention of tissue necrosis in patients with coronary artery disease might be implied. There is a body of clinical and experimental evidence to support this hypothesis.

The clinical evidence for the efficacy of propranolol in severe and intractable angina pectoris has been provided by a number of investigators. Initially Black and Stephenson[4] suggested that beta adrenergic blocking drugs might be useful in the management of patients with angina pectoris. On the basis of clinical studies, Keelan,[5] Fitzgerald and Grant [6] and Gianelly and colleagues[7] all reported a significant reduction in the number of anginal attacks, a decrease in the consumption of glyceryl trinitrate and an improvement in pain free effort tolerance of patients with angina pectoris treated with propranolol Furthermore Wolfson and associates[8] suggested that the incidence of sudden death and acute myocardial infarction in patients with severe and intractable angina pectoris was reduced in those treated with propranolol, compared to similar patients receiving traditional therapy or treated surgically with internal mammary implants. Similarly Mizgala and associates[9] were impressed by the relatively low incidence of sudden death and acute myocardial infarction in their coronary artery disease patients treated with propranolol

There are experimental data in both animals and man to explain these observations. In the dog Braunwald and Moroko[10] used epicardial mapping of S T segment elevation to define the extent of myocardial damage after experimental coronary occlusion In this circumstance propranolol reduced the extent of ischemic injury as reflected in a *decrease* in S T segment elevation resulting from the coronary occlusion, while isoproterenol infusion increased both the extent and severity of ischemia. In man Wolfson and Gorlin[11] have demonstrated that following the administration of propranolol, exercise results in a lesser increase in heart rate ventricular work, cardiac index, and pressure *time* per minute both in normal subjects and in patients with coronary disease Although propranolol administration increased ventricular volume which would tend to increase myocardial oxygen consumption, the over all effect of the drug was an attenuation in the increment of MVO_2 associated with exercise

These observations led us *to speculate* on the mechanisms through which withdrawal of propranolol might result in myocardial infarction. Coronary artery disease is generally accepted to be a progressive disorder Treatment with propranolol, by lowering myocardial oxygen requirements, may permit considerable progression of the disease without induction of myocardial damage In some patients, the coronary disease may *progress to* the point where resting oxygen requirements might not be met by the compromised coronary circulation in the absence of propranolol. In these patients, the abrupt withdrawal of propranolol therapy could result in myocardial infarction.

Annotations

A new bedside radioisotope test for the detection of deep-vein thrombosis

Pulmonary embolism is a tragic and not infrequently fatal occurrence in hospitalized patients. Approximately 2 700 persons die from pulmonary embolism in Great Britain and Ireland yearly. An association between pulmonary embolism and deep vein thrombosis (DVT) has been clearly documented.[1] If the incidence of pulmonary embolism is to be reduced it will be necessary either to prevent DVT or to detect it at a time when effective therapy may be introduced which will prevent pulmonary embolism.

A number of prophylactic methods are in use for the prevention of DVT: low dose heparin,[2] dextran,[3] hydroxychloroquine sulfate,[4] mechanical aids.[5] Each of these methods has been shown to reduce the incidence of DVT and hopefully future larger studies will show that one or a number of these methods is effective in reducing the incidence of pulmonary embolism.

Alternatively early diagnosis and treatment of DVT would lead to a reduction in the incidence of pulmonary embolism. Unfortunately the clinical diagnosis of DVT is notoriously unreliable. On the one hand it has been shown that in a group of patients with clinical signs of DVT 28 per cent were normal by the sensitive ^{125}I fibrinogen test.[6] On the other hand it has been reported that in 50 per cent of cases of pulmonary embolism clinical evidence of DVT is lacking.[7] Consequently if DVT is to be diagnosed prior to pulmonary embolism it will be necessary to screen large numbers of clinically normal hospitalized patients at frequent intervals, possibly daily. A number of techniques are presently being tried as a screening test for DVT: the ^{125}I fibrinogen test,[8] thermography,[9] electrical impedance,[10] ultrasound flow detection.[11] None of these tests to date is ideal as a mass screening test either because of inaccuracy in diagnosis or because of the complexity of the procedure or because the procedure carries a slight risk for the patient.

Therefore until a safe and effective prophylactic method for the prevention of pulmonary embolism is available or until a simple safe and accurate mass screening test for the detection of DVT is developed this common diagnostic and management question will continue to be asked in our hospitals: Does this patient have DVT and should anticoagulant or antithrombolitic therapy be started? To date x ray phlebography is the only method that will rapidly and accurately answer this question. A new bedside radioisotope test the ^{131}I MAA clearance test that my colleagues and I[12] recently reported as a preliminary communication in the *British Medical Journal* would appear to have application in this area. This radioisotope test uses a commercially available radiopharmaceutical ^{131}I labeled macroaggregates of albumin (^{131}I MAA) and equipment that is portable and inexpensive. The results are available in 20 minutes.

Labeled MAA has been in use as a lung scanning agent for more than ten years. In 1969 Webber and associates[13] reported that labeled MAA had an affinity for blood clots both in vivo and in vitro. A number of reports have appeared using this radiopharmaceutical in localizing venous thrombosis.[14,15] In these reports gamma cameras or rectilinear scanners have been used. Such equipment is expensive and presently is available only in the larger hospitals. The procedure requires the patient to be transported to the nuclear medicine department. It resembles in complexity x ray phlebography and so has no clear advantage.

It appeared to us that less sophisticated equipment might be adequate to detect ^{131}I MAA labeled thrombi since detection of the radioactive clot without accurately localizing the site and distribution of the radioisotope would be adequate to make a diagnosis. We have tried an inexpensive portable scintillation detector and rate meter that is in use in our department for the ^{125}I fibrinogen test (Pitman isotope localizing monitor). Acute femoral vein thrombosis was produced in 10 dogs by electrocautery. Approximately 20 to 30 μCi of ^{131}I MAA was injected intravenously distal to the clot. There was a 40 to 80 fold increase in count rate over the clot area when compared with sham control experiments, and this difference in count rate persisted for at least 20 minutes.

Fifty four patients with clinical signs suggestive of DVT have so far been investigated. Approximately 100 μCi of ^{131}I MAA was injected into the deep venous system using tourniquets. Count rates were obtained at five minute intervals for 20 minutes at seven points along the injected leg and at corresponding points on the opposite leg (control). The clearance of ^{131}I MAA from the injected leg fell into two easily discernible patterns: a rapid clearance pattern and a delayed clearance pattern. X ray phlebograms were performed in all 54 patients. Thrombi were identified in the leg veins in 34 patients and in 30 of these patients there was a delayed clearance of ^{131}I MAA from the leg (88 per cent). There were 20 patients in whom x ray phlebography failed to demonstrate thrombi and 17 of these the ^{131}I MAA cleared rapidly from the limb (85 per cent). Over all there was an 87 per cent agreement between positive phlebograms and delayed clearance and negative phlebograms and rapid clearance. These results suggest that this rapid, simple bedside radioisotope test may be adequate to answer this commonly encountered diagnostic problem: Has this patient deep vein thrombosis?

George J Duffy MD BSc MRCPI
Medical Director Isotope Department
St. Vincent's Hospital
Dublin, Ireland

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only therapy Can the very costly and labor intensive use of limited medical resources for a small group of relatively older patients be justified when a high risk of perinatal complications undernutrition, and lead poisoning continue to affect the quality of life of a significant proportion of our pediatric population? When chronic diseases such as asthma rheumatoid arthritis and diabetes are responsible for considerable morbidity among all ages? And when a more rational distribution of existing medical facilities and manpower could make basic medical care more accessible for all? With respect to coronary artery disease in particular using these same limited medical resources for research into the etiology of the disease and for the propagation of preventive measures—dietary changes and antismoking campaigns for example—would, by improving the life chances of a greater number of people earlier on, provide a greater net benefit to society as a whole

It is difficult for any physician to contemplate the prospect of denying an individual patient a therapy that might just work. We are arguing that physicians must develop a much broader frame of reference It is ultimately the case that one cannot assign a dollar value to any improvement in a person's life however slight however short But for the same reason we cannot continue to deny to the young and the disadvantaged the access to medical care that already exists for those who can afford to occupy the finite number of places for patients in the system. It is precisely because these kinds of decisions cannot be made by the individual practitioner that the society must develop a mechanism for making them It can no longer be the case that private interest determines how medical resources will be allocated. If such were to continue we would see the increasing proliferation of specialized forms of therapy for the few while increasing numbers of Americans are excluded from the benefits of present and future medical knowledge

Jonathan B. Kotch, M D *
Stanford University School of Medicine
Stanford, Calif 94305

Present address. King's College Cambridge England.

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The senile kidney

Physicians too frequently fail to recognize the senile kidney of old people The clinical manifestations are often subtle and resemble prostatism in the male and cystocele in the female In fact these latter illnesses are often considered to be responsible for the clinical manifestations when the etiology is senile kidney or arteriosclerosis of the kidney Surely the two diseases may coexist.

Senile kidney alone never kills With arteriosclerotic disease of the renal arteries there is some impairment of renal circulation but never enough to produce more than minor degenerative changes in the renal parenchyma and only slight changes in renal function Unless there is rupture of an arteriosclerotic plaque of the renal arteries with major obstruction to renal blood flow due to the plaque protruding into the lumen of a major renal artery and resulting in infarction or Goldblatt type of hypertension the elderly patient usually has senile kidney without ever knowing it

The impairment of renal function in senile kidney is minor There is mild hyposthenuria with maximal concentrating ability at 1 015 to 1 018 specific gravity There is some nocturia and frequency of urination. There may be traces of protein in the urine slight microscopic hematuria and a few fine coarse granular casts in the urine The total number of casts lost in the urine may be slightly greater than normal. Renal function is never sufficiently impaired to result in uremia The patient never dies of renal disease due to senile kidney itself Pathologically there are minor degenerative changes in all or any portions of the nephron due to old age and renal arteriosclerosis The arteries and small vessels do not show the changes characteristic of nephrosclerosis Arteriosclerosis of the kidney or senile kidney is quite different from nephrosclerosis

Senile kidney is a common renal disease a disease of almost all old people. It should be kept in mind when managing old people and it is particularly important in differential diagnosis.

Georg E. Burch, M.D
Department of Medicine
Tulane University School of Medicine
1430 Tulane Ave.
New Orleans La. 70112

As we have stated elsewhere[3] the association of myocardial infarction and withdrawal of propranolol may be a chance occurrence however the implications for a causal relationship are sufficient to warrant intensive clinical and experimental study In the interim when propranolol therapy is to be discontinued prudence would dictate that the dosage first be reduced in a decremental fashion

Ruth G Diaz M D
John Somberg
Ellen Freeman Ph.D
Barrie Levitt M D
Divisions of Cardiology and Clinical Pharmacology
Department of Medicine
New York Medical College
1249 5th Ave
New York N Y 10029

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The social context of coronary artery surgery

Recently tentative articles on the early outcome of saphenous vein bypass procedures for coronary artery occlusion have appeared in the literature I was moved by one article in particular[1] to consider in my own mind the usefulness of such costly and elaborate therapies in the context of what may be more pressing social and medical needs At the present time these considerations are subjective but hopefully the kind of data necessary to support the following argument will become available as the data from centers doing bypass procedures become more formidable

Up until now the reports of the outcome of coronary bypass procedures have been criticized for not being adequately controlled. Indeed, such a criticism has already appeared in this JOURNAL[2] However it is no longer sufficient merely to compare two therapeutic approaches to coronary artery disease with the assumption that whichever is proved superior must be adopted This common but naive attitude sees coronary artery disease in the social isolation of the university medical center A more complete evaluation of the two therapies must include a sophisticated comparison of the direct and indirect costs of both to the individual and to society Direct costs include the cost of prior and continuing research professional fees hospitalization and operating room expenses laboratory and so on Indirect costs include such parameters of morbidity as days lost from work as well as loss of staff and physical facilities to relatively more labor intensive surgical care These same research funds expenses for medical care staff and facilities might be used more profitably toward an entirely different medical problem It is at this level that the interests of society as a whole must be taken into account.

It is a challenging proposition in the United States that the society has an interest in the allocation of medical resources beyond that of the sum of the interests of a group of individuals We must first accept the fact that the proportion of the total cost of medical care paid out of government funds has increased dramatically since the passage of Titles XVIII and XIX (Medi Care and Medi Caid respectively) Furthermore the significance of federal money to medical research programs in this country cannot be denied as its relative scarcity these days all too painfully demonstrates. One may look at such funds as an investment that the society through its government has chosen to make in its medical care system Equally important is the notion that the system itself is a national resource and a strictly limited one at that. Both these sides of the issue the medical care system itself and the money available to it are becoming increasingly more public in effect if not in fact, and as such must be more responsive to the public s rather than the individual s needs.

Coronary bypass surgery is a good example of a situation in which these principles may be applied for in this case we have a very high concentration of medical resources for a very limited outcome As the criteria for eligibility for the procedure become more defined undoubtedly only a limited number of patients with coronary artery disease will in fact be candidates for surgery Of this select group many will be past their peak of socially productive work This would not in itself be a contraindication to pursuing bypass surgery if it were not undeniably the case that there still exist in America medical and social problems which affect a far larger number of people young or in the prime of life than are affected by debilitating coronary artery disease for which surgery is the

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Jonathan B. Kotch, M D
Stanford University School of Medicine
Stanford, Calif 94305

Present address King s College Cambridge England.

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George E. Burch, M D
Department of Medicine
Tulane University School of Medicine
1430 Tulane Ave.
New Orleans La. 70112

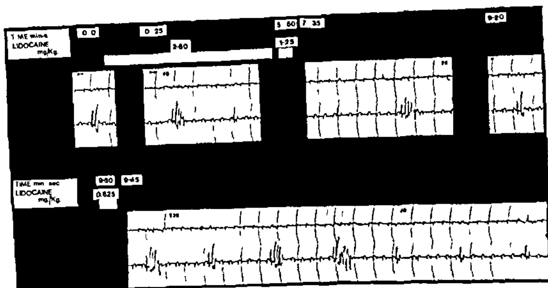


Fig 1

relatively large mass of electrically active but abnormal myocardium much of it subendocardial in distribution. Re entrant beats might originate in close proximity to the gates" as a result of inhomogeneous recovery of Purkinje and myocardial fibers, or within the affected myocardium it self Lidocaine has a relatively small effect on muscle action potential duration and it may be that higher tissue con centrations are required to abolish re-entry within the myocardium than in the region of the distal Purkinje fibers. Where the tissue concentration is relatively low lidocaine might promote or perpetuate re entrant activity by permit ting ultrapremature depolarizations originating in the resis tant subendocardial zone to escape through the now open gates. The observed abolition of decremental conduction would tend to prevent deterioration into fibrillation

The relative resistance to lidocaine of early ventricular dysrhythmias following myocardial infarction and the ad verse effect of lidocaine in some patients may be explained on this hypothesis if the site of re entry is remote from the sensi tive "gates as it must have been in the animal model The mechanism of the association between rapid heart rate and this adverse effect remains uncertain. The action potential durations at the gates must be shorter at rapid rates and this effect could summate with the lidocaine effect.

The antifibrillatory effect of lidocaine is not always ap parent in the clinical setting The onset of ventricular fibrillation has occasionally followed closely the intravenous administration of this drug While this may have been a chance occurrence we were particularly impressed by our observations of the effect of 200 mg of lidocaine ad ministered intravenously to a patient with myocardial in farction who was having frequent ventricular premature beats some minutes after the correction of ventricular fibrillation. The first 100 mg bolus had no effect but 2 minutes after a second similar bolus a brief episode of ventricular tachycardia heralded a 1½ minute period of uninterrupted sinus rhythm So far there was some parallel between the effects in this patient and experience with the dog re-entry model At the end of the 1½ minutes of absent ectopic activity ventricular fibrillation recurred without warning Careful control of lidocaine therapy is required and physicians using the drug should be aware that the effects are not always salutary The effects of low blood concentra tions for a time after conventional intramuscular adminis-tration or following an inadequate dose administered in travenously are potentially lethal

J S. Geddes B.Sc M D M R.C.P
S. W Webb B Sc M B M R C.P
A. A J Adgey M.B M R.C.P
Cardiology Department Royal Victoria Hospital
Belfast, Northern Ireland

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Reply

To the Editor

The letter by Dr Geddes and his associates calls attention to the very interesting phenomenon that lidocaine may not only fail to control ventricular arrhythmias in the very early stages following myocardial infarction but may in fact, have an adverse effect on cardiac rhythm in selected patients. The ability to reproduce this phenomenon in an experimental model is noteworthy The fact that lidocaine may shorten dramatically the action potential of subendocardial Purkinje fibers and thus eliminate a gating mechanism which might be viewed as protective against arrhythmias gener ated by the ischemic muscle is equally provocative

Despite the enormous interest over the past decade and a half in electrophysiology and electropharmacology of the myocardium it is a curious fact that only recently has atten tion been given to the study of actions of pharmacologic agents on ischemic tissues The fact that the action of phar macologic agents on ischemic tissue may be different from those on normal tissues and not be predicted by previous ex

Letters to the Editor

Specificity of early systolic notch

To the Editor

A recent article (Early systolic notch in the apexcardiogram in mitral stenosis, Becker L. C Klaus A P and Humphries J O N AM HEART J 86 582 1973) notes the occurrence of an early systolic notch in the apexcardiogram in mitral stenosis The authors state that this early systolic notch is nonspecific In a previous discussion (Clinical recognition of atrial myxoma Zitnik R S and Giuliani E. R AM HEART J 80 689 1970) we pointed out that this phenomenon in mitral stenosis (Fig 5) was generally associated with the sudden deceleration of blood moving toward the base when the valve apparatus (ring and pliable valves) reached its compliant limit Subsequent experience has confirmed this observation It is probable then that the occurrence of significant notching of the upstroke of the apexcardiogram may be an indication of good mobility of the stenosed mitral valve with sudden deceleration of the column of blood moving toward the base of the heart at the time of the opening snap and is thus *not* non specific as it implies a limited number of possibilities in terms of conditions associated with sudden oscillation(s) during isovolumic contraction

Ralph S Zitnik M D
2800 W 95th St.
Evergreen Park Ill. 60642

Reply

To the Editor

The authors agree with and appreciate Dr Zitnik s comments concerning the specificity and nonspecificity of the early systolic notch of the apexcardiogram We had used the term nonspecific to indicate that the presence of the notch was not seen *only* in patients with left atrial myxoma On the other hand we do agree with Dr Zitnik that the early systolic notch is seen only in certain hemodynamic situations and thus should bring to mind certain specific clinical disorders such as mitral stenosis with mobile mitral leaflets left atrial myxoma hyperdynamic states, etc

L. C Becker M D
A. P Klaus M D
J O Humphries M D
The Johns Hopkins Hospital
Baltimore Md. 21205

Effect of lidocaine on gating mechanism

To the Editor

The article by Wittig and colleagues[1] draws attention to the effect of lidocaine on the gating mechanism near the Purkinje myocardial junction which may normally prevent the most premature depolarizations on one side from spreading to the other Lidocaine in reducing the inhomogeneity of action potential durations partially removes the gates

The authors indicate the possible antiarrhythmic potential of this effect The effect described may however have equal significance in making understandable the adverse effect of lidocaine on frequency of ventricular ectopic beats which is not infrequently seen in patients with myocardial infarction treated within four hours of the onset of the attack[2] This adverse effect is in our experience confined to patients in whom the heart rate is over 90 per minute having been seen in five of 19 such patients treated by us. Among a total of 33 patients treated with a standard intravenous bolus of 100 mg of lidocaine followed by an infusion of the drug at a rate of 2 mg per minute lidocaine had either little effect or produced a less than 75 per cent reduction in frequency of ectopic beats during the subsequent 10 minutes in 16 These 33 patients included 14 whose rates were 90 per minute or less In addition to producing adverse effects lidocaine is thus frequently ineffective early in the attack.

Both pro and antiarrhythmic effects of lidocaine were easily demonstrated in an animal re entry model in which concentric warm and cold lesions were produced on the right ventricular wall of open chest mongrel dogs Premature stimuli were introduced through a unipolar electrode at the center of the lesion the warm area being immediately adjacent to this electrode It was possible to adjust the warm and cold temperatures in such a way that a single re-entrant beat usually resulted from premature and critically timed ventricular stimulation If more than one re-entrant beat occurred ventricular fibrillation was the almost invariable result. In two experiments intravenous lidocaine was administered The result of giving this drug in one of the experiments is illustrated in Fig 1 The tracings show bipolar electrograms from in the upper channel the right atrium and, in the lower channel the ventricles The atria were driven at a basic cycle length of 500 msec with after every sixth atrial stimulus a premature ventricular stimulus In the control situation the beat resulting from this premature stimulus was followed by a single re entrant beat Twenty five seconds after the beginning of the slow intravenous administration of lidocaine (2 5 mg per kilogram) multiple responses appeared which in contrast to the usual experience with this model, did not progress to fibrillation. Re entry then abruptly ceased A further intravenous dose of 1 25 mg per kilogram of lidocaine was given at 5 minutes 50 seconds When the effects of lidocaine were wearing off at 7 minutes 35 seconds a phase of multiple re entrant beats preceded a return to the control state (9 minutes 20 seconds) The reproducibility of the lidocaine effect is shown in the lower panel when a further small dose was given In the other experiment multiple responses without fibrillation were seen when test stimuli were applied following intravenous lidocaine 0 6 to 1 4 mg per kilogram with abolition of re entry following 1 7 mg per kilogram This biphasic response may be contrasted with the results of administering quinidine sulphate in this second experiment when re entry was reduced and then abolished at the test intervals at which it was previously elicited as the dose was increased to a total of 2 2 mg per kilogram without a single occurrence of multiple responses

Further experimental evidence for a dose related biphasic effect of lidocaine is provided by Spear and associates[3] Ventricular fibrillation threshold was invariably higher at high blood levels and often lower at low blood levels than the control value

In the light of the findings of Wittig and co workers, it may be possible to explain our clinical and experimental findings. Following coronary occlusion there is for a few hours a

Work carried out by one of us (J S. G) in collaboration with J A. Abildskov M.D at the University of Utah College of Medicine Cardiovascular Division

Book Reviews

Complex Electrocardiography Guest editor Charles Fisch M D Philadelphia 1973 F A. Davis Co 332 pp Price $15 00

This is an interesting book on electrocardiography Some of the complex ECG of conduction disturbances and arrhythmias constitute the major portion of the book. For example among the subjects discussed are concealed conduction, fascicular block exit block supernormality and electrolytes and the electrocardiogram This volume of Cardiovascular Clinics is another good one Cardiologists internists and electrocardiographers will find this a valuable book to study and own The ECG are well selected and well illustrated. The tracings and accompanying tests will require careful study They are too complex to permit casual reading

Clinical Hypertension. Norman M Kaplan M D New York 1973 Medcom Inc 347 pages

Kaplan has produced a valuable book on hypertension for the clinician The book is one of the Medcom Update Series This publication is intended for the practicing physician It brings together the present concepts of diagnosis and management of hypertension one of the most common and important illnesses of men Kaplan has included the common problems namely clinical approach to the patient with high blood pressure and its many special problems. He of course discussed effectively essential hypertension the renoangiotensin system renal disease hypertensive encephalopathy renovascular hypertension aldosteronism low renin hypertension the pill and others There are many well chosen illustrations diagrams and tables The present interest in this disease and the high incidence of hypertension make this fine book timely Physicians who have been in practice for many years and who have not followed the advancements closely will find many parts of the book difficult and meaningless to them Nevertheless the discussions are accurate and also reflect the author s interest Kaplan has been concerned with hypertension for several years particularly renovascular hypertension and the renoangiotensin system The reader will also learn the importance of office practice in the management of hypertension from the book He will learn of the many conflicts of opinion and observations which still exist today Nevertheless the sick patient cannot wait until these problems are resolved. He must be treated properly and effectively Fortunately he can with the present antihypertensive agents available especially if the hypertension and cause are detected early This is a good addition to an important field.

Cardiology D G Julian M.D London, 1973 Baillière Tindall & Cox Ltd. 431 pages Price $9 75

This second edition by Julian of Cardiology is a practical simple and clear discussion of the common problems in cardiology The discussions are intended for the practicing clinician. The illustrations are simple They clarify the accompanying text with sharp illustrations very well. The author emphasizes the bedside approach to the patient. The opinions and practices of the author are readily evident He integrates his own ideas with those of others effectively This is a small concise and well written practical book on clinical cardiology

Manual on artificial organs Yukihiko Nose M D Ph D St. Louis 1973 The C V Mosby Company 350 pages Price $37 25

This is a well illustrated and clearly presented discussion of the present day oxygenators used in artificial organ surgery and transplant surgery The contributors are from the Cleveland Clinic Nose is Director of the Department of Artificial Organs at the Cleveland Clinic Nose s book should interest all surgeons and medical associates who participate in cardiovascular surgery Kidneys liver and the heart are among the organs discussed most extensively i e next to whole man. This is a valuable contribution to cardiovascular surgery and to transplantation surgery

perimental studies on normal tissues opens an entire new and important area for investigation. Furthermore it seems highly likely that the nonuniform effects of pharmacologic agents which have been observed even in normal tissues may be amplified in the presence of alterations in the distribution of these agents as a consequence of coronary arterial obstructive disease The observations by Dr Geddes are extremely important and they should provide an important stimulus to re evaluate some of our hypotheses about the mechanisms of arrythmias after myocardial infarction and the action of pharmacologic agents Hopefully provocative observations such as these will lead to new experimental designs to clarify the many major and still unresolved questions about arrhythmias and their treatment following myocardial infarction

Andrew G Wallace M D
Duke University Medical Center
Durham N C 27710

Hemoptysis caused by pulmonary venous obstruction

To the Editor

I have somewhat belatedly come across the excellent discussion by Drs. Haroutunian and Neill[1] of hemoptysis in congenital heart disease To their list which includes both cardiac and vascular anomalies one should add pulmonary *venous obstruction Venous obstruction does indeed result* from such lesions as cor triatriatum perhaps associated with hemoptysis more often in older patients, which they did note than in children More severe lesions causing high grade obstruction can produce the same complication in childhood

Several years ago we described stenosis presumably congenital of the individual pulmonary veins in a 6 year old child with severe recurrent hemoptysis[2] Unexplained bleeding of bright red blood from bronchial mucosa was severe enough to justify a partial pneumonectomy in a desperate but futile attempt to stay the disease The surgeon observed that the azygous and intercostal veins were dilated and pulsating It was only later at postmortem examination that we discovered the cause of the problem to be extreme constriction of the pulmonary veins at their junctions with the left atrium *The source of pulmonary bleeding was bronchial* mucosal varices which represent anastomotic connections between pulmonary and systemic veins Pulmonary veins communicate with bronchial vessels both deep within the lung and at the hilus[3] Deep bronchial vessels drain centrally to connect with pulmonary veins and sometimes directly with the left atrium[3] the hilar bronchial veins connect to systemic veins[3]—azygous intercostal innominate—possibly accounting for some of the anomalous connections observed in patients with venous hypertension[4] Becker and associates[5] have shown dilated bronchial veins in the lungs of six of 13 infants with pulmonary venous obstruction in half of them markedly dilated bronchial veins were present deep in the parenchyma and impinged upon bronchial lumens. *Andrews[6] noted a history of hemoptysis in three of four* adults with differing types of acquired pulmonary venous occlusion With shunts of great magnitude extravasation can be responsible for life threatening hemoptysis.

In a similar way communications between the intrapulmonary and the systemic veins allow the development of collateral circulation in adults with acquired mitral stenosis.[7] Distended bronchial mucosal vessels have long been implicated in pulmonary hemorrhage in such patients, although the distinction between arterial distention and venous varices has not always been clear[8] Interesting in a historical sense has been the application of these observations to the relatively successful use of surgical pulmonary systemic shunting in cases of mitral stenosis and venous hypertension to decompress the lesser circulation.[9]

Jay Bernstein, M D
Director Department of Anatomic Pathology
William Beaumont Hospital
Royal Oak Mich. 480[illegible]

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Editorial

Malignant hypertension

Frank A Finnerty Jr M D
Washington D C

It has been hypothesized that malignant hyper tension may be a reversible disease and that sur vival may be possible if life can be maintained for a reasonable period while healing of the ar teriolitis is occurring[1] It has also been observed that patients with malignant hypertension par ticularly those with renal insufficiency fre quently die during the early stages of treatment before the benefits of remission can be realized.[1] We have therefore adopted the policy of treat ing all patients in the accelerated phase of hyper tension with or without papilledema as medical emergencies as vigorously and aggressively as those with hypertensive encephalopathy[2]

In essence the aim of therapy is to keep the diastolic pressure under 100 mm Hg and the urinary output over 2 liters per day In our expe rience these goals can usually be attained by in termittent repeated intravenous injections of diazoxide and orally administered furosemide The indication for further diazoxide or hydral azine (a constant infusion of *sodium nitro prusside* or intermittent intramuscular injec tions of hydralazine) is the return of the diastolic pressure to 100 mm Hg Repeated injections of diazoxide or hydralazine are continued until a single injection keeps the diastolic pressure under 100 mm Hg for more than 24 hours

Diazoxide is available in 20 m ampules 5 mg per milliliter The average effective dose is 300 mg (1 ampule) In our experience (over one thou sand treated patients) 95 per cent of adult pa tients respond to this dosage In the child with encephalopathy due to acute nephritis or in the adult who weighs more than two hundred pounds or in any situation where one ampule of diazoxide does not produce the desired fall in ar terial pressure the dosage of diazoxide should be 5 mg per kilogram The optimum antihyperten sive effect of diazoxide is noted in one to two minutes No individual titration of dosage is nec essary As a matter of fact studies from this laboratory have demonstrated the necessity of administering the full dosage in a bolus—within ten seconds—if the optimum effect is going to be assured.[3]

Nitroprusside is administered by a constant in fusion drip containing 0 04 to 0 06 mg per milli liter The rate of infusion is regulated according to the level of the blood pressure Its disadvan tages are the lack of availability commercially (soon to be corrected) the necessity to prepare a fresh solution and the need for titrating the dosage which requires constant monitoring Although hydralazine can be administered by muscle it has a relatively rapid onset of action e g 30 to 40 minutes it is less potent than the other two rapidly acting agents. The frequent ap

From the Department of Medicine Georgetown University School of Medicine and the Georgetown University Medical Division District of Columbia General Hospital, Washington D C. 20003

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Reprint requests to Dr Frank A. Finnerty Jr Department of Medicine The Georgetown University Medical Division, District of Columbia General Hospital Washington, D C 20003

Announcements

Pathology of congenital heart disease

A two to eight week training program in the pathology of congenital heart disease is being offered by the Departments of Pediatrics and Pathology of The Johns Hopkins University Physicians currently enrolled in postgraduate training programs as well as those who have completed training are eligible to apply Trainees will have the opportunity to study specimens from a collection of over 700 hearts with congenital malformations and to correlate clinical data with the defects, including history phono vector and electrocardiograms radiographs angiograms operative notes and autopsy reports The trainees also will be encouraged to attend conferences and rounds in the Departments of Pediatrics Medicine Surgery Radiology and Pathology and to discuss cases at the weekly Pediatric Cardiology Conference

A per diem allowance is offered to physicians currently enrolled in a residency or fellowship training program For further information please write to Dr Glenn C Rosenquist, Department of Pediatrics The Johns Hopkins Hospital 601 North Broadway Baltimore Md 21205

George von Hevesy prize for nuclear medicine

George von Hevesy was a pioneer of nuclear medicine For his studies in the field of radioactive indicator technique he received the Nobel Prize in 1943 He was one of the founders and honorary president of the Society of Nuclear Medicine (Europe)

At the First World Congress of Nuclear Medicine held in Tokyo from Sept 30 until Oct. 5 1974 under the presidency of H Ueda M D the George von Hevesy prize for nuclear medicine will be awarded again The prize amounts to 10 000 Swiss Francs

Unpublished scientific papers, preferably in English but accepted also in German and French on the subject of nuclear medicine can be submitted by authors up to the age of 40 years The papers should be restricted to a maximum of eight typewritten pages Upon decision of the Committee of Trustees the prize can be divided. The manuscripts should be received before Aug 10 1974 by Prof Dr W Horst, Clinic of Nuclear Medicine University of Zurich Rämistrasse 100 8006 Zürich Switzerland

Since each of these unfavorable effects on the kidney is greatly enhanced in patients with azotemia it is readily understandable why reduction of arterial pressure in these patients has consistently aggravated the degree of azotemia frequently produced congestive heart failure and hastened the patient s downhill course

The availability of furosemide and the reports of its beneficial effects in high doses[6 7] particularly in azotemic patients suggested that combining it with diazoxide or hydralazine might do away with at least some of the detrimental effects of acute reduction of arterial pressure in hypertensive azotemic patients Furosemide by itself has a modest effect on the arterial pressure a varying effect on the cardiac output and sodium excretion (Fig 1)[8] Administering these agents together produces a greater decrease in arterial pressure than that from diazoxide alone increases cardiac output and increases urinary sodium excretion and urinary output

In 1967 Woods and Blythe[1] concluded that the reduction of arterial pressure in patients with malignant hypertension complicated with azotemia did not necessarily result in deterioration of renal function and might result in improved survival rates Studies in our laboratory have demonstrated that more aggressive reduction of the arterial pressure while maintaining urinary output and preventing sodium retention further improved survival rates in such patients

We feel that the beneficial results in these patients with accelerated phase hypertension are not peculiar to diazoxide or furosemide but seem best explained by the physiologic hemodynamic effects accompanying the reduction in arterial pressure that is increase in cardiac output decrease in total peripheral resistance increase in urinary output, and prevention of sodium retention Although other parenterally administered agents e g hydralazine or nitroprusside may be used in combination with furosemide the lack of potency and frequent side effects associated with hydralazine and the difficulty in preparation and administration of nitroprusside limit their usefulness

Limitations of diazoxide and furosemide

Although the immediate onset of action maintenance of cardiac output increase in urinary output and sodium diuresis and lack of significant side effects make the combination of diazoxide and furosemide extremely valuable for the treatment of accelerated hypertension it does have certain limitations

1 The alkaline nature of the diazoxide solution makes any extravasation outside the vein painful Although such extravasation is associated with a severe burning sensation which lasts from one to two hours no sloughing of tissues has occurred

2 Although the fall in arterial pressure following the administration of diazoxide alone is not associated with postural hypotension the addition of furosemide to diazoxide by decreasing the plasma volume commonly produces postural hypotension[9] Awareness of the possibility of this complication and maintenance of the supine position is all that is necessary

3 Transitory hyperglycemia lasting no more than twelve hours frequently follows the intravenous administration of diazoxide A recent report of Wolff Grant and Wales[10] and studies done in our laboratory[1] have demonstrated that pretreatment of patients with tolbutamide will effectively prevent the hyperglycemic effect of diazoxide Diazoxide is not contraindicated in patients with diabetes It would seem however that when diazoxide is administered for more than a 48 hour period, the blood sugar level should be monitored closely If significant increases in blood sugar occur tolbutamide can then be added

4 The nausea and vomiting are probably related to the muscle relaxing properties of diazoxide which include the stomach as well as the uterus Withholding food two hours before and after the administration of diazoxide has kept the incidence of vomiting to under 10 per cent in our experience

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	DIAZOXIDE	FUROSEMIDE	DIAZOXIDE + FUROSEMIDE
MAP	↓↓	↓	↓↓↓
CO	↑↑	↓↑	↑↑
SODIUM BALANCE	(+)(+)	(−)(−)	(−)
URINARY OUTPUT	↓↓	↑↑	↑

Fig 1 Effects of diazoxide furosemide and diazoxide and furosemide on mean arterial pressure cardiac output sodium balance and urinary output

pearance of headache flushing, and tachycardia further limits its usefulness

Furosemide is at least 25 times as potent as the thiazide diuretics Equally important is the observation that its potency may be further increased by increasing the dosage The ability to tailor the dosage to the individual situation and to exert its effect in the face of electrolyte imbalance favors the use of this agent as the prime therapy in patients with accelerated phase hypertension When doses above 160 mg are needed we have obtained better results with once a day administration When urinary output cannot be maintained above 1 000 ml per day peritoneal dialysis should be combined with furosemide and repeated as often as necessary This combination may well tide the patient over a critical period and prevent the development of end stage" renal failure In our experience the lack of ability to maintain adequate urinary output despite increasing doses of furosemide is the best clinical sign of deterioration of renal function

When a single injection of diazoxide has kept the diastolic pressure under 100 mm Hg for more than 24 hours or preferably a few days sooner, oral antihypertensive agents e g , methyldopa in multiple doses of 250 mg , four times a day (beginning with 250 mg once a day) or hydralazine in multiple doses of 25 mg three or four times a day (beginning with 25 mg twice a day) are instituted Since guanethidine decreases cardiac output and decreases renal blood flow and glomerular filtration rate more than the other antihypertensive agents, we feel that it is contraindicated in azotemic patients. Furosemide is continued in reduced dosage e.g., 80 to 160 mg per day

The prompt clearing of papilledema and decrease in retinopathy, the significant reduction in serum creatinine three months after such therapy, and the improvement in renal blood flow and glomerular filtration rate in the majority of the subjects we have followed, all adequately attest to the reversibility of the malignant phase of hypertension[3] Such data support the plea for aggressively treating patients in the accelerated phase of hypertension before renal vascular deterioration has proceeded beyond the point of no return Although such patients should be thoroughly investigated to rule out curable types of hypertension (if a satisfactory therapeutic response is not obtained), it is suggested that therapy be instituted first and investigations performed after the arterial pressure has been controlled

Aggressive therapy should not be discontinued because of a rise in BUN or creatinine, since such rises are usually transitory and due to a hemodynamic alteration rather than further damage to the kidney Determinations of inulin and PAH clearances three months later have usually significantly improved above control values Serial determinations six and twelve months later have shown continued improvement. Renal biopsies performed in seven patients six months after control of the arterial pressure have demonstrated healing of the necrotizing arteriolitis[4] It may be argued that gradual reduction (instead of acute reduction) of arterial pressure might prevent even this transitory worsening of renal function In our opinion the imminent danger of a cerebral vascular accident in these patients demands emergency treatment. Experience in our clinic and that of others[5] has demonstrated (1) the high incidence of cerebral complications when the arterial pressure is not under control, (2) the longer the arterial pressure is uncontrolled, the greater the danger of cerebral complications and (3) the grave prognosis once a cerebral complication has occurred.

Lowering the arterial pressure with most potent antihypertensive agents (except for the diuretics) is accompanied by a decrease in renal blood flow glomerular filtration rate, urinary output and an increase in sodium retention

Clinical communications

Vectorcardiographic comparison of left ventricular hypertrophy in idiopathic hypertrophic subaortic stenosis aortic stenosis and aortic regurgitation

Thomas A Brackbill M D
Pravin M Shah M D *
Rochester N Y

Hypertrophy is an important adaptation to a chronic increase in work load by the left ventricle[1 2] The increase in work load may represent an increase in either pressure work or volume work The fundamental difference in the pattern of hypertrophy which results from pressure overload (concentric hypertrophy) from the pattern occurring in volume overload (eccentric hypertrophy) has long been recognized from anatomic and pathologic studies[1 3] and in more recent years has been appreciated during life by left ventricular angiography[4 5] Cabrera and coworkers[6 7] introduced the concept that the type of hemodynamic overloading was reflected in characteristic differences in electrocardiographic and vectorcardiographic appearance They proposed that the vectorcardiographic Q loop increases in magnitude in diastolic (volume) overloading and decreases or disappears in systolic (pressure) overloading of the left ventricle

In contrast to hypertrophy resulting from an increase in either pressure work or volume work patients with primary cardiomyopathies have myocardial hypertrophy which is not the result of any demonstrable increase in work load In one specific pathophysiologic form of this disorder—idiopathic hypertrophic subaortic stenosis (IHSS)—characteristic asymmetric hypertrophy of the interventricular septum is invariably present[8 9]

Our present study was undertaken to determine if spatial vectorcardiography might have a role in distinguishing between the concentric hypertrophy of aortic stenosis the eccentric (volume overload) hypertrophy of severe aortic regurgitation and the asymmetric septal hypertrophy of IHSS If a distinguishing vectorcardiographic pattern of left ventricular hypertrophy in IHSS were found this technique might become a valuable adjunct in the diagnosis of this disorder complementing the echocardiographic[10 12] means of diagnosis There is good theoretical reason to postulate that spatial orientation and magnitude of vectorial forces would be *different* in these three conditions which produce widely varying degrees and locations of increments in left ventricular muscle mass In aortic valve disease an increase in muscle mass resulting from increased work is proportional to the severity of the valve lesion However the bizarre asymmetric hypertrophy is almost invariably seen in all clinically recognized cases of IHSS irrespective of the severity of left ventricular outflow obstruction at rest Indeed the latter is dynamic and often quite variable The present study was undertaken to explore the use of spatial vectorcardiography in a series of patients with the three broad types of hypertrophy documented by hemodynamic and angiographic studies

F om th C rdı logy Un t, Dep rtme t f Med cın Un e ty of Rochester Medı al Center Roch te N Y

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*Th w k w don durıng Dr Shah tenur of n Am rı an H art Assoc at on T ach ng Sch la Awa d.

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Table II

	0 01 sec			0 02 sec			0 03 sec		
	Magnitude	Azimuth	Elevation	Magnitude	Azimuth	Elevation	Magnitude	Azimuth	Elevation
AR 20 cases									
Mean	0 217	86 4	− 0 06	0 477	66 3	6 35	0 894	10 2	20 4
SD	0 124	81 7	37 8	0 248	72 2	28 6	0 471	56 6	19 5
SE	0 028	18 3	7 73	0 055	16 1	6 40	0 106	12 7	4 35
AR vs AS	p < 0 01	NS	NS	p < 0 05	NS	NS	NS	NS	NS
AS 25 cases									
Mean	0 130	72 1	−15 4	0 341	42 3	2 58	1 07	0 316	18 1
SD	0 049	80 5	34 7	0 158	59 3	25 8	0 392	34 9	12 7
SE	0 010	19 0	6 95	0 032	11 9	5 17	0 078	6 97	2 54
AS vs IHSS	NS	NS	S	NS	NS	NS	NS	NS	NS
IHSS 21 cases									
Mean	0 153	78 5	− 9 59	0 403	50 7	7 34	0 813	5 24	23 7
SD	0 106	87 3	37 0	0 268	84 4	32 4	0 542	48 7	23 7
SE	0 023	16 1	8 28	0 059	18 4	7 24	0 118	10 6	5 17
AR vs IHSS	NS	NS	NS	NS	NS	NS	NS	NS	NS

The following calculations were then computed

(1) Magnitude of the instantaneous spatial vector at each 10 msec interval and of the maximal spatial vector according to the Pythagorean theorem

$$S_V = \sqrt{x^2 + y^2 + z^2}$$

(2) Azimuth of each instantaneous vector according to the formula

$$H = +\tan^{-1} \frac{z}{x}$$

(3) Elevation of each instantaneous vector according to the formula

$$V = +\tan^{-1} \frac{y}{\sqrt{x^2 + z^2}}$$

The following convention was used For elevation horizontal left was zero degree horizontal right was ± 180 inferior vertical was +90 and superior vertical was −90 Regarding azimuth horizontal left was zero degree horizontal right was ± 180 anterior was +90 and posterior was −90 (Fig 1)

Results were obtained for azimuth elevation and magnitude of the spatial vector at each 10 msec interval from 0 010 sec through 0 070 sec for each patient Within each group results were correlated with age of the patients Group means for each group (IHSS AS and AR) were compared by means of an unpaired T test

Results

The results for each group at each interval are seen in Tables II through IV Table II lists the results of the initial 0 01 to 0 03 sec vectors

The 0 01 sec vector The largest magnitude was found in the AR group and differed significantly ($p < 0\ 01$) from the group with AS The IHSS group had a magnitude of intermediate value The azimuth in AR was slightly but not significantly more rightward than in IHSS or AS

The 0 02 sec vector The magnitude in AR was again significantly ($p < 0\ 05$) larger than in AS Again magnitude in IHSS was intermediate There were no significant differences in either elevation or azimuth

The 0 03 sec vector The largest magnitude was found in the AS group and the smallest in IHSS The differences were not significant The results of the 0 04 0 05 and maximal spatial vectors can be seen in Table III

The 0 04 sec vector The magnitude of the AS group remained largest and differed significantly ($p < 0\ 02$) from IHSS The magnitude for AR was slightly less than for AS No significant differences in azimuth or elevation were noted

The 0 05 sec vector The magnitude of the AR group was significantly larger ($p < 0\ 01$) than that of IHSS AS was intermediate in magnitude No significant differences were noted in azimuth or elevation

Maximal spatial vector The magnitude of the AR group was largest The AS and IHSS groups had almost identical magnitudes and the difference between AR and the other two groups was not significant Azimuth and elevation did

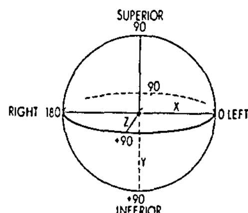


Fig 1 Diagram depicting orientation and positivity of the X, Y and Z orthogonal axes

Table I

Lesion	Total	Male	Female	Age	
				Mean	Range
IHSS	21	9	12	48 0	17 78
AS	25	20	5	55 0	25 77
AR	20	13	7	37 7	16 65

Methods

Sixty six patients ranging in age from 16 to 78 were included in this study Twenty one had IHSS 25 had aortic valve stenosis and 20 had aortic regurgitation The age and sex distribution for each group is summarized in Table I

Routine diagnostic cardiac catheterizations included right and left heart studies the latter being either by transeptal approach or retrograde technique Cardiac outputs were determined by standard indicator dilution technique using indocyanine green An assessment of the severity of valve lesions in patients with AS or AR was based on pressures flows and angiographic data Coronary arteries were visualized either by Judkin's or Sone s technique or, in some patients from adequate left heart angiography

Eighteen of the 21 patients with IHSS were demonstrated by cardiac catheterization to have left ventricular outflow obstruction either at rest or after provocation (postectopic beat Valsalva maneuver amyl nitrite isoproterenol etc) The three remaining cases had the characteristic echocardiographic findings of IHSS with abnormalities consistent with outflow obstruction [10] All the patients with aortic valve stenosis had peak systolic gradients across the valve of ≥ 50 mm Hg Those with accompanying significant aortic regurgitation were excluded. Aortic regurgitation was assessed to be moderate to severe in all patients with isolated aortic regurgitation included in this study based on aortic root angiograms.

Patients in each group with associated mitral valve disease or significant pulmonary hypertension ($\overline{PA}$ ≥ 35 mm Hg) were excluded to avoid the effects of co existent right ventricular hypertrophy Similarly patients with significant coronary artery disease demonstrable by angiography were excluded

Vectorcardiograms were obtained in the supine position utilizing a Hewlett Packard vector programmer and the Frank lead system with the chest electrodes at the level of the fourth intercostal space Polaroid pictures of each loop were obtained at high sensitivity (0 1 mv per centimeter) for initial forces as well as at standard sensitivity The dash time interval was 2 5 msec Patients were included in this study only if vectorcardiograms were of sufficient technical quality to allow accurate identification of the very earliest QRS forces in each plane Nine patients with IHSS whose earlier vectorcardiograms had not included adequate blow ups of the initial forces were recalled for repeat vectorcardiographic study In all of the remaining patients in each group the vectorcardiogram was obtained within 24 hours of the cardiac catheterization and angiography

The QRS duration was determined for each loop and the highest value found was taken as the patient s QRS duration All patients whose total QRS duration was ≥ 0 12 sec or who had complete left bundle branch block (LBBB) or right bundle branch block (RBBB) were excluded from analysis Each planar loop was then analyzed in detail with particular attention paid to accurate identification of the very earliest QRS forces The 10 20, 30 40 50 60 and 70 msec planar vectors were identified in each loop The projection of each 10 msec instantaneous vector onto the X Y, and Z coordinates was then measured Care was taken to assure that the dashes corresponding to each 10 msec interval were consistent from one loop to the next For instance the dash representing the 20 msec. vector in the horizontal plane will have the same intercept on the X axis as does the 20 msec vector of the frontal plane In this way identity of dash times from one loop to the next could be determined

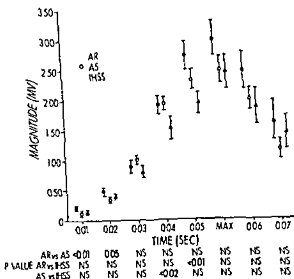


Fig 2 The magnitude of the instantaneous mean spatial vectors in aortic regurgitation (AR) aortic stenosis (AS) and idiopathic hypertrophic subaortic stenosis (IHSS) Figures depict mean value in millivolts (MV) ± the standard error (S E.) The P value for each interval is shown at the bottom NS = not significant.

0 04 sec. when AS was largest At no time was the magnitude of IHSS greater than that of the other two groups

Fig 3 represents the mean azimuth for each group No significant differences were observed It should be noted that the mean azimuth at 0 01 sec was in the left anterior quadrant i e was less than +90 for each group One would expect that normal septal depolarization would have resulted in a 0 01 sec vector which was directed anteriorly and to the right Part of the reason for this apparent discrepancy can be better understood by referring to Fig 4 This demonstrates that the effect of having a few instantaneous vectors located in the right posterior quadrant (between −90 and −180°) is to shift the entire group mean to the left toward zero Thus two extremely rightward vectors whose signs are opposite such as +170 and −170 when averaged arithmetically yield an extreme leftward vector zero degree When each individual vector at 10 and 20 msec is plotted out graphically as in Fig 4 it can be seen that indeed most patients in each group did show the expected rightward and anterior initial forces

Discussion

Although the vectorcardiographic characteristics of left ventricular hypertrophy have

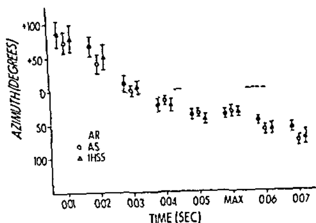


Fig 3 The azimuth of the instantaneous mean spatial vectors in aortic regurgitation (AR) aortic stenosis (AS) and idiopathic hypertrophic subaortic stenosis (IHSS)

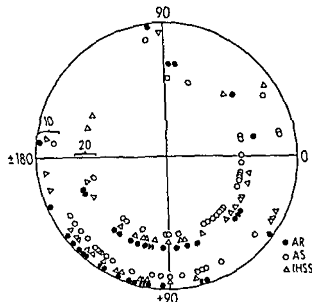


Fig 4 Individual azimuths at 10 msec (outer ring) and 20 msec (inner ring) for patients with AR AS and IHSS Note that in each group a few patients have initial vectors located in the left posterior quadrant (see text)

been the subject of numerous previous studies[13-17] relatively few[15,16] have sought to compare the findings in pressure loaded ventricles with those of volume loaded ventricles The concept of distinctive patterns of ventricular overloading proposed by Cabrera and co workers[6,7] has not met with wide acceptance in part because of a lack of confirming hemodynamic and autopsy data Its value appears to be greatest in congenital heart disease[18] while in adults with acquired left ventricular hypertrophy considerable over

Table III

	0 04 sec			0 05 sec.			Maximal spatial vector		
	Magnitude	Azimuth	Elevation	Magnitude	Azimuth	Elevation	Magnitude	Azimuth	Elevation
AR 20 cases									
Mean	1 92	-21 1	26 9	2 72	-37 2	25 0	2 98	-37 4	22.5
S D	0 790	36 0	12 6	1 02	26 6	13 4	1 16	26 2	13 5
S E	0 177	8 04	2 81	0 229	5 95	2 99	0 259	5 87	3 05
AR vs AS	NS	NS	NS	NS	NS	NS	NS	NS	NS
AS 25 cases									
Mean	1 95	-16 0	21 7	2 31	-35 6	18 6	2 48	-32 7	17 1
S D	0 440	27 7	12 0	0 727	25 1	19 1	0 714	33 4	16 8
S E	0 088	5 55	2 41	0 145	5 03	3 82	0 143	6 69	3 35
AS vs IHSS	p < 0 02	NS	NS	NS	NS	NS	NS	NS	NS
IHSS 21 cases									
Mean	1 52	-22 0	24 6	1 92	-43 3	16 8	2 47	-34 4	17 4
S D	0 700	32 2	16 6	0 827	32 2	16 0	1 08	36	16 0
S E	0 153	7 02	3 62	0 180	7 02	3 50	0 235	7 86	3 50
AR vs IHSS	NS	NS	NS	p < 0 01	NS	NS	NS	NS	NS

Table IV

	0 06 sec			0 07 sec		
	Magnitude	Azimuth	Elevation	Magnitude	Azimuth	Elevation
AR 20 cases						
Mean	2 45	-48 8	18 3	1 63	58 2	11 7
S D	1 36	22 4	14 9	1 32	31 7	21 7
S E	0 304	5 02	3 33	0 296	7 10	4 85
AR vs AS	NS	NS	NS	NS	NS	NS
AS 25 cases						
Mean	1 97	-59 8	9 09	1 14	-77 7	5 02
S D	0 811	30 8	25 2	0 636	35 1	26 5
S E	0 162	6 15	5 04	0 127	7 01	5 30
AS vs IHSS	NS	NS	NS	NS	NS	NS
IHSS 21 cases						
Mean	1 84	-58 8	6 59	1 43	-71 4	-3 53
S D	1 10	37 5	20 5	1 37	43 2	29 6
S E	0 240	8 19	4 47	0 300	9 43	6 45
AR vs IHSS	NS	NS	p < 0 05	NS	NS	NS

not differ significantly The time of occurrence of the maximal spatial vector did not differ significantly among AS (49 6 msec) IHSS (51 4 msec) and AR (51 5 msec) The results of the 0 06 and 0 07 sec vectors can be seen in Table IV

The 0 06 sec vector No significant differences were noted in either magnitude or azimuth The mean elevation in IHSS was significantly ($p < 0.05$) more superior than in AR

The 0 07 sec vector The magnitude in AR remained largest but did not differ significantly from the other groups No significant differences in azimuth or elevation were noted

Mean QRS duration The mean QRS duration was determined for each group This was shortest in AS (88 2 msec) intermediate in IHSS (91 7 msec) and longest in AR (93 9 msec) These differences were not statistically significant.

Effects of age on spatial QRS vector No significant correlation was found in any group between advancing age and any of the vectorcardiographic parameters studied.

Fig 2 represents the mean magnitude of each of the three groups of patients at each 10 msec interval and at the time of the maximal spatial QRS vector (V Max) It should be noted that the magnitude of the AR group exceeded that of AS or IHSS at all except two intervals 0 03 sec and

anatomic left ventricular hypertrophy The so called pseudo infarction pattern noted in early reports[34 36] is felt to be secondary to depolariza tion of the hypertrophied septum resulting in ac centuation of the normal pattern of initial left to right septal activation Recently several re ports[38] have re emphasized the importance of dis tinguishing the deep Q waves of IHSS from the pathologic Q waves of myocardial infarction especially in the elderly population In our series of 21 adult patients with IHSS only two patients displayed a pattern of pseudo infarction on elec trocardiogram or vectorcardiogram

The marked septal hypertrophy of IHSS is out of proportion of the moderate hypertrophy of the lateral free wall Yet our vectorcardiographic studies did not yield electrical manifestations of this hypertrophy Ferrans Morrow and Roberts[29] in a detailed histologic study of myofibrillar architecture in the hypertrophied septum of patients with IHSS have emphasized the bizarre disarray which the fibers exhibit They speculate that the force developed by a group of diversely oriented cells would be less than that of a similar number of cells which were in an orderly linear arrangement It is the lat ter situation which one would anticipate in con centric and eccentric hypertrophy resulting from pressure or volume overload Just as the mechan ical forces of any individual fiber in IHSS may be subject to much internal cancellation by adjacent nonparallel fibers it is tempting to speculate that perhaps the electrical manifestation of asym metric septal hypertrophy as recorded by the sur face electrocardiography and vectorcardiogra phy may also be blunted by analogous forms of electrical internal cancellation within the sep tum

Summary

Frank vectorcardiograms in 21 patients with idiopathic hypertrophic subaortic stenosis and asymmetric septal hypertrophy (IHSS) 25 pa tients with severe aortic valve stenosis (AS) and 20 patients with severe aortic regurgitation (AR) were analyzed Patients with mixed valvular le sions pulmonary hypertension coronary artery disease or QRS width $\geq$ 0 12 sec were excluded The QRS loops were analyzed at 10 msec inter vals (0 01 to 0 07 sec) and mean spatial vectors were derived. Spatial magnitude azimuth and elevation were measured. The magnitudes of the 0 01 and 0 02 sec vectors were significantly larger in AR than in AS ($p < 0\ 01$ and $p < 0\ 05$ respectively) The magnitude of the midloop vec tors (0 04 sec) was largest in AS ($p < 0\ 02$) while the 0 05 sec vector was largest in AR ($p < 0\ 01$) No significant differences in azimuth elevation time of maximal spatial vector or QRS duration were noted among the three groups Only two of 21 patients with IHSS demonstrated the pattern of pseudo infarction In the remaining patients, the analyzed vectors failed to distinguish the asymmetric septal hypertrophy of IHSS from the concentric hypertrophy of AS

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lap of patterns has been found both in clinical[19] and autopsy[3] studies raising doubts about the specificity and usefulness of the concept

In a study designed to evaluate the validity of Cabrera s postulates Toshima Cueto and Lillehei[15] examined 92 patients with acquired mitral and aortic valve disease Using the Schmidt Simonsen (SVEC III) method of vector cardiography spatial QRS vectors were derived for patients with pure lesions of aortic regurgitation aortic stenosis and mitral insufficiency as well as mixed lesions Their findings in the groups with pure AR and pure AS tended to confirm Cabrera's postulates the magnitudes of the 0 01 and 0 02 sec and maximal spatial vectors were greatest for aortic regurgitation while the 0 03 and 0 04 sec vectors were greatest for aortic stenosis The longest QRS intervals were found in the aortic regurgitation group

The findings in this study using the Frank orthogonal vector system are in close agreement with those of Toshima Cueto and Lillehei[15] Significantly larger QRS magnitude was observed at both 0 01 and 0 02 sec in AR compared to AS Moreover these forces were directed slightly more rightward in AR corresponding to the Q loop of Cabrera s diastolic overload pattern At 0 03 and 0 04 sec the AS voltage was larger but not significantly Both maximal voltage and QRS duration were greatest in the AR group Thus our data as well as that of Toshima Cueto and Lillehei[15] suggests that the trends of Cabrera s postulates tend to be fulfilled when large groups of patients in each category are compared The wide degree of scatter noted in the data for each of the groups of patients would limit the usefulness of these postulates however when attempting to apply them to individual patients

Vectorcardiographic[20] and electrocardiographic[21] studies of normal adult populations have demonstrated that maximal QRS voltage tends to decline with age However, McCall Wallace and Estes[22] observed only minor differences among the five decades over the age of 20 years In the present study regression analysis comparing age with spatial QRS magnitude revealed no correlation in any of the three groups Thus it is unlikely that age played a significant role in the greater spatial magnitudes noted in the AR group

Several patients in each group had 0 01 and 0 02 sec instantaneous vectors which were oriented posteriorly and to the left Since all patients in this study were free of significant coronary artery occlusions this abnormal orientation of the initial forces indicates the effect of the left ventricular hypertrophy *per se* Thus our findings support the recent studies of Hilsenrath and co workers[23] who emphasized the unreliability of using posteriorly directed initial forces to diagnose myocardial infarction in the presence of the left ventricular hypertrophy These are at variance with the earlier findings of Hugenholtz, Forkner, and Levine [24]

Hugenholtz and Gomboa[25] have applied the anatomic findings of Linzbach[1] in an explanation of the diminished Q loop seen in pressure overloading of the left ventricle The increased number of myocardial fibers present in the inner layer of the left ventricular outflow tract produces an increased electrical contribution by these forces to the over all electrical activity of depolarization Moreover, these forces exert their influence from the very earliest portion of the QRS thus partially canceling the simultaneously occurring rightward septal forces An alternative explanation, that of incomplete left bundle branch block, is unlikely, since the mean QRS duration in our study was less in AS than in AR findings which were also noted by Toshima Cueto and Lillehei [15] In volume overloading on the other hand the dilation of the left ventricular cavity permits a relative delay in the activation of the free wall of the left ventricle allowing the early septal forces to remain prominent, without cancellation by the free wall forces The longer QRS duration found in the AR group is consonant with this hypothesis

Previous studies in several other forms of congenitally determined heart disease have led to the recognition of distinctive vectorcardiographic patterns In Duchenne s progressive muscular dystrophy [26 27] in supravalvular aortic stenosis [28] and in 46XX or XY Turner phenotype [29] unusual patterns of ventricular depolarization have been observed In contrast our analysis of patients with IHSS and striking asymmetric septal hypertrophy failed to reveal a distinctive vectorcardiographic pattern

The electrocardiographic pattern of left ventricular hypertrophy is frequently observed in patients with IHSS [30-32] although relatively few studies have sought to compare its pattern in that disorder with the pattern in other types of

The prognostic significance of the ballistocardiogram in ischemic heart disease

Thomas N Lynn M D
Oklahoma City Okla

Stewart Wolf M D
Galveston Texas

The purpose of the present study was to explore further the possible utility of the ballistocardiogram (BCG) in the evaluation of patients with ischemic heart disease and especially to test in a prospective way over a ten year period, the prognostic value of repeated ballistocardiographic tracings

One attractive feature of the BCG is that it is a noninvasive technique that can be repeated as often as desired in the same individual While it has not been possible to relate abnormalities in the BCG pattern to specific cardiovascular lesions or syndromes or to obtain quantitative data on certain conventional hemodynamic measures the BCG has proved of value as it reflects the force of cardiac ejection As such in studies by Starr and Schroeder[1-4] more than 30 years ago it yielded the only objective evidence of heart disease in subjects having suffered a myocardial infarction in the past Confirmation followed from several laboratories[5-8] The effects of lipidemia on the BCG in patients with ischemic heart disease were reported by Kuo and Joyner[9] and the effects of hypoxia by Penneys[10] In 1946 Starr[11] reported a striking prognostic capability in the BCG in ischemic heart disease More than half of a group of subjects over age 50 whose BCG s were abnormal were found to have suffered myocardial infarctions at follow up eight years later while only 3 per cent of those with initially normal BCG s had evidence of heart disease eight years later[11] Baker and co workers[12] reviewed a nine year experience with the prognostic capability of a single BCG They found than an abnormal record was associated with an increased risk of subsequent myocardial infarction in both healthy subjects and those with ischemic heart disease

Fr m the T tts Gap Inst tute Bango Pa nd th Department of Commun ty H alth Un ty of Okl hom Health Sc n e Ce ter Oklahom City nd th M rine B omed c l I st tute Univ rsity of T as M dical B a ch, Gal ton

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Materials and methods

There were 134 subjects in all of whom 67 (53 men and 14 women) had had a myocardial infarction at intervals varying from two months to six years in the past The patients were drawn from a consecutive series of patients seen at the University of Oklahoma Medical Center between 1962 and 1965 Selection was made only on the basis of geographic proximity to Oklahoma City None of the patients declined to participate The diagnosis of myocardial infarction was established by unequivocal electrocardiographic changes and elevated SGOT at the time of their acute attack The other 67 subjects were apparently healthy control subjects drawn from more than 1 000 candidates in two industrial firms and the State Highway Department. They were selected to match individually with the patients on the basis of age (± 2 years) sex, race height (± 2 inches) weight (± 8 pounds) educational background (years of schooling) and type of job The ages are reported as of September 1962 the time of the first set of predictions (Table I) The age range extended from 25 to 80 years The average age for the whole group was 53 Seventy one per cent of the subjects were below age 60 BCG s were recorded on each of the subjects both patients and controls approximately six times a year over a two to seven year

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waves the prominence of diastolic waves and, to a lesser extent on the presence of respiratory variation in the HIJ complex and on lengthening of the interval between the Q wave of the electrocardiogram and the I and J waves of the BCG (QI and QJ intervals)

Results

Thirty five of the patient group and two of the control subjects died during the ten year period of study The deaths of two of the patients and the two control subjects were unrelated to heart disease Two others of the patient group committed suicide Ten individuals survived recurrent myocardial infarctions but only four of them survived the entire ten year period of study Thirty one of the patients died of definitely established or presumed acute myocardial infarction Of those 22 were autopsied Acute infarcts were found in 10 and only an old myocardial infarction in the other 12 Eight of the 31 coronary deaths had entered the study after the 1962 prediction period and died before the 1966 prediction period Therefore they and their matched controls were dropped for the purposes of this report, leaving 118 as the total number of patients and controls This comprised the study group and included 23 subjects (16 men and 7 women) who died of definitely established or presumed myocardial infarction Seventeen were autopsied Fresh infarcts were demonstrated in eight and only old scars in the other nine The four individuals who survived recurrent myocardial infarction during the period of study and the two suicides are also included in the study group (Table I)

Effect of age The average age of those correctly predicted was 55 9 and of false positives 53 8 while the average age of those who died or had recurrent infarcts without having been predicted was 54 7 Thus it was inferred that the predictions were not biased by the likelihood of death merely on the basis of age

Statistical analysis The likelihood of chance selection was tested for each of the predictors according to the combinatorial probability formula [13] It yields a probability of exactly k successes in a random sample of size n drawn without attention to the order of selection from a population of M subjects in which D experience a cardiac event The formula written in factorial symbols is as follows

$$P = \frac{\binom{D}{k}\binom{M-D}{n-k}}{\binom{M}{n}} \; *$$

M = total number of subjects
n = total number of subjects predicted to die or suffer a myocardial infarct
D = total number of events (myocardial infarction or death)
k = total number of correctly predicted events
$\binom{D}{k}$ = combination of D subjects taken k at a time

Sixteen from among the subjects available for prediction in 1962 died of definitely established or presumed myocardial infarction during the subsequent period of the study Eight of them were among the 10 on the BCG prediction list The other two on the prediction list were the two who committed suicide

On the 1966 list there were four false positives out of the 10 predicted Seven deaths and two recurrent infarcts were missed. There were four individuals who were missed in both the 1962 and 1966 predictions. Thus there were a total of 14 correct predictions out of 20 tries The probability of chance selection was less than 0 001

Summary and conclusions

In a prospective study of patients with ischemic heart disease and matched control subjects BCG records of the acceleration type were obtained over a two to seven year period at approximately bimonthly intervals Predictions of subsequent myocardial infarction or sudden death based on a qualitative assessment of the BCG pattern were highly accurate at the 0 001 level of confidence

* Also written $\frac{C^D_k \, C^{M-D}_{n-k}}{C^M_n}$

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Table I

Subject age	*Sex*	*No*	*Entered study*	*Death or M I.*	*Autopsy*
Correct predictions					
47	M	001	12/61	10/62	Old scar
63	M	002	2/62	2/67	Old scar
66	M	003	1/62	3/64	Old scar
60	F	006	10/61	3/68	Old scar
46	M	007	10/61	10/67	–
59	M	008	11/61	8/64	Old scar
45	M	014	1/62	6/66	
74	F	016	1/62	1/68	Fresh M.I.
68	F	017	2/62	9/65	Fresh M I.
50	M	020	2/62	7/66	Fresh M.I
64	F	021	3/62	12/66	Old scar
51	M	034	5/62	2/67	
49	M	042	10/62	7/69	Fresh M.I.
41	M	086	5/64	4/66	Fresh M.I
False positives					
52	M	015	1/62		
41 control	M	100	10/61		
58 control	F	135	1/63		
66 control	F	140	3/63		
Suicides					
55	M	022	3/62	9/62	
51	F	023	3/62	3/63	
Missed					
65	M	005	10/61	7/63	–
44	M	010	12/61	1/67	–
66	M	013	1/62	4/65	–
70	F	018	2/62	1/65	Old scar
78	F	024	3/62	11/69	–
35	M	031	5/62	3/66	Fresh M I
32	F	035	7/62	11/66	Fresh M I
50	M	048	11/62	7/66	
44	M	052	4/63	2/68	
59	M	054	4/63	8/68	Fresh M.I
58	M	063	7/63	12/69	–
44	M	078	11/63	6/66	Old scar
67	M	099	2/62	2/64	Old scar

Recurrent myocardial infarction

period of prospective study A total of 2 858 tracings were made on the 134 subjects yielding an average of 21 3 records per individual

After one year of study those 10 subjects whose BCG s displayed the greatest abnormality were identified and their names placed in a closely guarded prediction file on the assumption that they had the poorest prognosis with respect to recurrent myocardial infarction or sudden death Four years later additional predictions were made to include those subjects who had entered the study after the first list was made

The instrument used was an air suspended ultra low frequency model having a natural frequency of 0 184 cycles per second and manufactured by Astrospace Laboratories The acceleration of head to foot movement was recorded on a Grass polygraph via a crystal diode accelerometer The table was balanced by adding lead bricks The subject was always tested in mid morning without having smoked and at least two hours postprandial Any medications were recorded with the time of the last dose A simultaneous electrocardiogram lead was also recorded The tracings were rated by a single cardiologist on a 0 to 4 scale 0 being entirely normal Increments 1 through 4 were based on the degree of lowering and splintering of the HIJ

Ventricular function curves from the cardiac response to angiographic contrast A sensitive detector of ventricular dysfunction in coronary artery disease

Bruce H Brundage M D LTC MC
Melvin D Cheitlin M D COL MC F A C C
Washington, D C

The assessment of ventricular function in coronary artery disease is of paramount interest to the cardiologist and surgeon when selecting patients for coronary artery surgery The left ventricular (LV) cineangiogram with the detection of areas of dysynergy as well as the determination of ejection fraction has been used to assess the state of LV function Depressed ventricular function is associated with increased mortality in coronary artery surgery and therefore its critical evaluation is mandatory [1]

Numerous investigators have noted that the left ventricular end diastolic pressure (LVEDP) rises following LV angiography and that there is some correlation between the degree of elevation and the severity of LV dysfunction as well as the extent of coronary artery disease [2-9] However controversy continues as to whether elevation of the LVEDP is produced by contrast induced depression of myocardial contractility or by increase in venous return produced by the osmotic effect of the contrast media The purpose of this paper is to report on these hemodynamic responses to a standard LV angiogram in a group of normal individuals and a group of patients with severe coronary artery disease The sensitivity of ventricular function curves derived from the hemodynamic response contrast will be evaluated and compared with ejection fraction and resting LVEDP more standard methods of evaluating ventricular function

Methods

Forty four patients were studied by right and left heart catheterization for evaluation of coronary artery disease Six patients were restudied three to six months following coronary artery saphenous vein bypass surgery All catheterizations were performed in the postabsorptive state and patients were premedicated with 50 mg of meperidine and 25 mg of phenergan Patients taking digitalis and/or propranolol had these drugs discontinued at least five days and two days respectively before the catheterization No patient included in the study had valvular or primary myocardial disease

LV cine angiograms were performed by injecting 0 8 c c per kilogram or 60 c c (whichever volume was less) of methylglucamine diatrizoate (Renografin 76) through a pigtail catheter over four seconds LV and aortic pressures were recorded on an Electronics for Medicine DR 12 recorder immediately prior to and three to four minutes after the angiogram through a saline filled polyurethane or polyethylene pigtail catheter connected to a P23Db Statham strain gauge LV pressures were recorded on photographic paper at speeds of 75 mm and 200 mm per second and at sensitivities of 50 mm and 200 mm Hg full screen The first derivative of the LV pressure (dp/dt) was recorded with an RC differentiator Aortic pressure was recorded at a speed of 75 mm per second and a sensitivity of 200 mm Hg full screen Cardiac outputs were measured prior to and three minutes after LV

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Table I

Parameter measured	Group A N = 13 Before angio	After angio	P value for paired Student's t test	Group B N = 14 Before angio	After angio	P value for paired Student's t test
LVEDP (mm Hg)	8 5 ± 0 6	16 1 ± 1 1	< 0 001	12 9 ± 1 7	25 6 ± 1 5	< 0 001
Cardiac index (L/min/M²)	3 0 ± 0 3	3 7 ± 0 4	< 0 01	3 2 ± 0 3	3 5 ± 0 3	< 0 10 NS
Heart rate	75 ± 3	73 ± 2	< 0 50 NS	80 ± 3	83 ± 4	< 0 60 NS
SVI (ml/beat/M²)	40 3 ± 3 9	52 8 ± 4 0	< 0 01	38 2 ± 2 7	40 1 ± 1 2	< 0 40 NS
LVSP (mm Hg)	105 7 ± 3 7	117 8 ± 3 7	< 0 02	106 9 ± 5 9	113 7 ± 5 0	< 0 20 NS
SWI (Gm M/M²)	52 9 ± 5 2	70 8 ± 5 9	< 0 001	47 7 ± 5 0	45 6 ± 3 0	< 0 50 NS
ΔP/ΔV (mm Hg/ml)	0 17 ± 0 02	0 18 ± 0 02	< 0 70 NS	0 29 ± 0 04	0 42 ± 0 04	< 0 01
Vce max $\left(\frac{dp/dt}{IP \times 32}\right)$	0 92 ± 0 06	0 82 ± 0 04	< 0 05	0 86 ± 0 06	0 73 ± 0 04	< 0 02
dp/dt max (mm Hg/sec)	1 617 ± 93	1 925 ± 129	< 0 001	1 585 ± 122	1 784 ± 109	< 0 01
dp/dt/40 mm Hg DP	34 5 ± 1 6	37 7 ± 2 1	< 0 05	31 8 ± 1 8	35 8 ± 1 9	< 0 01
V max (lengths/sec)	1 17 ± 0 08	1 13 ± 0 05	< 0 40 NS	1 10 ± 0 05	1 00 ± 0 05	< 0 20 NS

SVI = str k v lum nd x LVSP = left ntr cul r sy tolic p ssure SWI = strok work ndex ΔP/ΔV = change in LV diastolic p essure/ troke lum V e = loc ty co tr ctil l ment. IP = isov lum pres ure DP = de el ped pressu e NS = not s g ificant.

not significantly change in either group Dp/dt max increased by 308 mm Hg per second in Group A and by 199 mm Hg per second in Group B This change was highly significant in both groups Dp/dt/40 mm Hg developed pressure increased significantly after angiogram in both groups

Ventricular function curves The sensitivity of the left ventricular function curve determined from the hemodynamic response to contrast in detecting abnormality was compared to other measures of ventricular function in 37 studies in 31 patients with significant coronary artery disease This portion of the study includes the 14 patients in Group B and additional individuals with coronary disease who had ventricular function curves developed but no measurements of contractility or compliance made To determine a range of normal the ventricular function curves of the 13 patients (Group A) with no detectable heart disease were plotted (Fig 1) In all subsequent figures the shaded area will represent the range of our normals All these individuals had ascending ventricular function curves LVEDP s of less than 12 mm Hg prior to LV angiogram and normal ejection fractions (greater than 0 55)[16]

The patients with significant coronary artery disease also had ventricular function curves constructed from the hemodynamic response to contrast They were divided into two groups by their ejection fraction Nine out of 12 (75 per cent) with ejection fractions of 0 55 or less had a ventricular function curve outside normal range (Fig 2) Abnormal ventricular function curves were also demonstrated in 11 out of 25 (44 per cent) of coronary artery disease patients with normal ejection fractions (> 0 55) (Fig 3)

Coronary artery disease patients with resting LVEDP s of greater than 12 mm Hg had abnormal ventricular function curves in 9 out of 11 (82 per cent) instances (Fig 4) Abnormal ventricular function curves were observed in 12 out of 26 (46 per cent) of the patients with a normal LVEDP (Fig 5)

Discussion

Controversy continues about the hemodynamic events following LV angiography[17,18] There is good evidence that the hyperosmotic contrast

angiogram by indocyanine green dye or thermodilution indicator techniques [10,11]

Following all hemodynamic measurements coronary arteriography was performed by the Judkins technique [12] Significant coronary artery disease is defined as 50 per cent or greater narrowing of the diameter of one or more major coronary arteries

LVEDP was measured at the onset of rapid pressure rise after the A wave If this point was indistinct the pressure was measured 0 05 second after the onset of the Q wave of the electrocardiogram [13] The end diastolic pressure represents the average of all beats recorded during one respiratory cycle Stroke work index was calculated by the formula

$$SWI = \frac{(LVSP - LVEDP) \times SVI \times 1\ 36}{100}$$

The mean left ventricular systolic pressure (LVSP) was determined by planimetry of the area under the aortic pressure curve during systole Stroke volume index (SVI) was obtained by dividing the cardiac index by heart rate

In 13 patients (Group A) with normal coronary arteriograms and no evidence of left ventricular dysfunction and in 14 patients (Group B) with severe coronary artery disease and markedly impaired LV function the following additional measurements were made before and three to four minutes after angiogram Compliance ($\Delta P/\Delta V$) was obtained by dividing the difference between left ventricular end systolic and end diastolic pressure by the stroke volume Stroke volume was determined by dividing the cardiac output by heart rate [14] Force velocity curves were developed from LV dp/dt by the formula

$$Vce = \frac{dp/dt}{IP \times 32} \quad [15]$$

IP = isovolumic pressure Peak Vce V_{max} dp/dt max and dp/dt/40 mm Hg developed pressure were determined

Ejection fractions were calculated in all patients by the area length method from a single plane right anterior oblique view [16] Ventricular function curves were constructed in all 50 studies by plotting the stroke work index against the LVEDP before and three to four minutes after the ventricular angiogram

The severity of disease and dysfunction in Group B is attested to by the facts that these patients had an average ejection fraction of 0 43 and an average of 2 4 vessels significantly obstructed This was a very symptomatic group of patients as 10 of the patients underwent coronary artery surgery The postbypass patients in Group B had a total of 12 grafts of which 9 (75 per cent) were occluded

Results

In an attempt to delineate the mechanisms involved in the rise in LVEDP pressure after LV angiogram and to determine why this rise is greater in patients with significant coronary artery disease than in individuals with normal ventricular function two groups of patients were evaluated for changes in contractility and compliance Group A included 13 individuals who were undergoing coronary arteriography because of an abnormal electrocardiogram or a history of chest pain Their right and left heart catheterization coronary arteriogram and LV angiogram were normal The 14 patients in Group B had significant coronary artery disease (average 2 4 vessels significantly involved) poor LV function (average EF 0 43), and were very symptomatic (10 out of 14 had bypass surgery) This group was selected on the basis of a very abnormal response to angiographic contrast ie there was little to no rise or a decreased stroke work index in association with a rise in LVEDP pressure after left ventricular angiogram

LVEDP rose significantly after angiogram in both groups but to a greater extent in Group B (Table I) Cardiac index increased by 0 7 L per square meter in Group A but the increase in Group B was not significant There was no significant change in heart rate in either group Left ventricular mean systolic pressure increased 10 mm Hg in Group A and 7 mm Hg in Group B however the change was only statistically significant in the former Stroke work index increased by 18 Gm meters per square meter in Group A and by the selection as previously stated was unchanged in Group B The pre angiogram $\Delta P/\Delta V$ in Group A (0 17) was significantly lower than in Group B (0 29) $p < 0\ 05$ Also there was a significant decrease in compliance after angiogram in Group B

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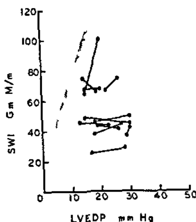


Fig 4 Ventricular function curves from the hemodynamic response to contrast in patients with coronary artery disease and abnormal resting LVEDPs (> 12 mm Hg) CAD = coronary artery disease LVEDP = left ventricular end diastolic pressure SWI = stroke work index

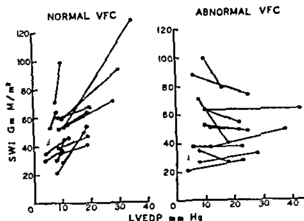


Fig 5 Ventricular function curves from the hemodynamic response to contrast in patients with coronary artery disease and normal resting LVEDPs (= or < 12 mm Hg) CAD = coronary artery disease LVEDP = left ventricular end diastolic pressure SWI = stroke work index VFC = ventricular function curve

contractility as measured by max dp/dt/P with a micromanometer tip catheter

We were also interested in investigating the mechanisms for the greater increase in LVEDP after contrast media in patients with significant coronary artery disease compared to the normal patients [9,20] To do this we made the same hemodynamic measurements in a group of patients (Group B) with severe coronary artery disease who demonstrated a smaller increase in cardiac index (0 3 L per square meter) but a marked increase in LVEDP (13 mm Hg) i e they had flat or descending ventricular function curves In this group there was a significant decrease in $\Delta P/\Delta V$ after angiogram but no significant change in V_{max} The increase in dp/dt max and dp/dt/40 mm developed pressure and a decrease in peak Vce are consistent with large change in preload seen in this group [21,22]

This data would imply that the marked increase in LVEDP after angiography in patients with severe coronary artery disease is due to the increased stiffness of the LV and not to a decrease in contractility The ventricle in the coronary artery disease patients was significantly less compliant ($p < 0.05$) than the normal ventricle (0 17 vs 0 29) This would place the ventricles with coronary artery disease at the upper end of the nonlinear compliance curve so that small increases in venous return would result in greater increases in LVEDP [26] We demonstrated that the cardiac index increased slightly but the change was not statistically significant. Other than some decrease in peak Vce we found no evidence of decreased contractility following LV angiogram at the time measured (3 to 4 minutes) in either normal ventricles or those with severe coronary artery disease Those investigators who have reported a decrease in myocardial contractility following LV angiogram have usually made their measurements in the first postangiogram minute [23,27-30] The hemodynamic event that most likely explains the rise in LVEDP after angiogram is an increase in intravascular volume and, therefore venous return as a result of the hyperosmotic effect of contrast media on extravascular fluid. Ventricles with normal compliance may respond to the increased venous return produced by the osmotic load of angiographic contrast by increasing LVEDP and consequently cardiac output (the Frank Starling mechanism) Stiff ventricles such as those with severe coronary artery disease (CAD) could be expected to show a greater elevation in LVEDP in response to an increase in venous return It has also been suggested that these less compliant ventricles do not stretch as much for equivalent increases in filling pressure and, therefore demonstrate depressed Frank Starling ventricular function curves [26] This thesis would be consistent with our observations in patients with severe CAD (Group B)

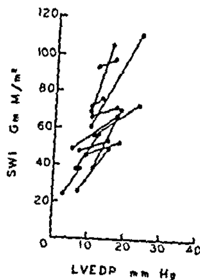


Fig 1 Ventricular function curves from the hemodynamic response to contrast in 13 patients with no evidence of heart disease LVEDP = left ventricular end diastolic pressure SWI = stroke work index

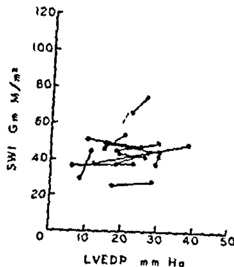


Fig 2 Ventricular function curves from the hemodynamic response to contrast in patients with coronary artery disease and abnormal ejction fractions (EF is less than 0 55) CAD = coronary artery disease LVEDP = left ventricular end diastolic pressure SWI = stroke work index

media produces an increase in blood volume and cardiac output following angiography [7,9] It is also well known that the LVEDP increases after the use of contrast media [9,20] What is not clear is whether this elevation is due to an increase in venous return a decrease in myocardial contractility, or a change in ventricular compliance In order to better understand these changes a number of hemodynamic measurements were made before and after LV angiogram in a group of essentially normal individuals (Group A)

A significant increase in LVEDP and cardiac

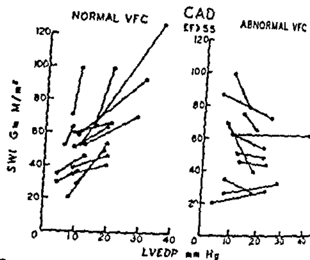


Fig 3 Ventricular function curves from the hemodynamic response to contrast in patients with coronary artery disease and normal ejection fractions CAD = coronary artery disease LVEDP = left ventricular end diastolic pressure SWI = stroke work index VFC = ventricular function curve

index was demonstrated (Table I) but there was no significant change in V_{max} or compliance ($\Delta P/\Delta V$) Dp/dt max increased very significantly and this is explainable on the basis of the increase in preload a factor known to increase dp/dt max [21] Dp/dt/40 mm developed pressure also increased significantly and a significant decrease in peak Vce was demonstrated but these also could be explained by the rather marked increase in preload [22] Others have suggested, because of diminished or no change in hemodynamics after infusion of equivalent volumes of an equally hypertonic glucose solution that there must be a decrease in left ventricular contractility to account for the observed changes after contrast [23,24] Cohn and coworkers[24] made a comparison of ventricular function curves obtained from the response to angiographic contrast and isosmotic isovolumic infusions of glucose in 10 patients The response was similar in six patients but 4 patients with flat function curves with contrast had ascending curves with hypertonic glucose The authors concluded that there must be some decrease in contractility after angiographic contrast However our data would suggest that in individuals with normal ventricular function, the increase in LVEDP after angiography is brought about by an increase in venous return and not by changes in contractility or compliance Bush Lewis, and Fontana[25] also found no significant change in

ventricular end diastolic pressure (LVEDP) and stroke work index (SWI) before and three to four minutes after a standard left ventricular angiogram In an attempt to delineate the mechanism that produces changes in the post angiogram LVEDP and SWI 13 individuals (Group A) with no evidence of cardiac disease were compared to 14 patients with severe coronary artery disease (Group B) Cardiac output and LVEDP increased in both groups after angiogram The increase in cardiac output was less and the increase in LVEDP greater in Group B V_m did not change significantly after angiogram in either group Other measures of contractility (dp/dt max peak Vce and dp/dt/40 mm developed pressure) changed appropriately for the large changes in preload seen after angiogram

Thirty seven studies in patients with coronary artery disease demonstrated that VFC obtained from the cardiac response to contrast are more sensitive than resting LVEDP or ejection fraction in detecting left ventricular abnormality

VFC can be obtained from the ventricular response to angiographic contrast because of the increase in venous return produced by the hyperosmotic effect of contrast Depressed curves occur in patients with coronary artery disease because of their stiff ventricles and not because of depression of myocardial contractility

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Some comment about the methods by which force velocity relationships were determined is justified All pressure measurements were made through a saline filled catheter connected to an external pressure manometer The *inaccuracies* of this system are well known However the purpose of this study was oriented more toward detecting directional changes in these relationships rather than absolute values Other investigators have reported that the fluid filled catheter system is sensitive enough to detect changes in force velocity relationships [31,32]

Since the major hemodynamic effect of the injection *of radiographic contrast into the cardiovascular* system seems to be an increase in the volume of blood presented to the left ventricle it would appear valid to construct ventricular function curves from this response In addition to the previous comments about compliance, it should be noted that the left ventricular systolic pressure does increase slightly more after angiogram in normal ventricles than in those *with severe coronary artery disease but this* should not detract from the usefulness of these ventricular function curves Indeed the range of the ventricular function curves obtained in our normal subjects (Group A) correlates well with a group of normal subjects reported by Ross and Braunwald [33]

Comparison of the sensitivity of ventricular function curves derived in the described manner with other measurements of ventricular function in detecting abnormalities has confirmed that these curves are useful and sensitive (Figs. 2 through 5) The resting LVEDP is an often used measurement of ventricular function When it exceeds 12 mm Hg it usually indicates significant left ventricular dysfunction Yet it is often known to be normal in the face of serious coronary artery disease Predictably a high percentage (9 out of 11, 82 per cent) of patients with abnormal resting LVEDP s had abnormal left ventricular function curves However nearly half of the patients *(12 out of 26) with significant* coronary artery disease and normal resting LVEDP s had abnormal ventricular function curves

The ejection fraction calculated from the left ventricular angiogram is now commonly used to assess ventricular function Values less than 0 55 are usually considered *abnormal* [16] Abnormal ventricular function curves were obtained in 75 per cent (9 out of 12) of patients with an abnormal ejection fraction A significant number of patients with normal ejection fractions and coronary *artery* disease also demonstrated abnormal ventricular function curves (11 out of 25 44 per cent) Only one patient with both an abnormal resting LVEDP and abnormal ejection fraction had a ventricular function curve that could be construed as normal Indeed this curve was outside the range of normals but was ascending and it was not considered valid to call it an abnormal function curve These observations would imply *that the ventricular function curve derived from* the hemodynamic response to contrast is more *sensitive than the* ejection fraction or resting LVEDP in detecting ventricular dysfunction. It must be stated however, that the ejection fractions were calculated by the area length method from a single plane right anterior oblique cineangiogram and that use of the biplane technique may have been more sensitive Neverthe*less the single plane technique* has been reported to correlate well with biplane techniques [34]

Cohn and co workers[24] have also reported that contrast induced ventricular function curves demonstrate a high degree of sensitivity in detecting abnormal function in coronary artery disease patients with *normal* resting dynamics.

The ventricular function curve derived from the response to angiographic media used in ventriculography appears to be a sensitive detector of LV dysfunction The measurements are easily made before and after the ventricular angiogram especially with the advent of easily obtained *thermodilution cardiac* output. LV angiography is performed in nearly every patient undergoing coronary arteriography prior to bypass surgery and many are studied postoperatively to assess graft patency Therefore ventricular function curves constructed in the described manner should be a *helpful adjunct in determining* the effects of this operation on the left ventricle

Summary

Fifty cardiac catheterizations were performed *in 44 patients* undergoing *evaluation* for coronary artery disease Ventricular function curves (VFC) were constructed by plotting the left

A new temporary pacing catheter with improved sensing and safety characteristics

Thomas A Preston MD FACC
Seattle Wash.

Temporary artificial cardiac pacing is a fully accepted procedure with widespread application The indications for temporary pacing are numerous[1,2] but most temporary pacing is done for acutely ill patients who have bradyarrhythmias or tachyarrhythmias Two serious manifestations of pacing failure are (1) inadequate demand (standby) pacer sensing of spontaneous beats leading to competitive pacing[3,4] and (2) stimulation during the vulnerable period of the preceding beat leading to pacer induced ventricular tachycardia or fibrillation[5,6]

It is the acutely ill patient with myocardial infarction hypoxia or metabolic imbalance who is in jeopardy of improper pacing Because of the recurrent problem of inadequate sensing in temporary pacing systems[3,4,7] and the infrequent but potentially fatal complication of competitive pacing (pacemaker induced ventricular arrhythmia)[5,6] there is a need for a safer pacing electrode system that can avoid these complications This report describes a unipolar pacing catheter that is designed to give improved sensing and a decreased likelihood of pacer induced arrhythmia even in the presence of competitive pacing One electrode (cathode) is at the distal tip of the catheter and the other electrode (anode) is 23 cm proximal to the distal tip The improved sensing derives from widely spaced electrodes and the decreased risk of arrhythmia is a result of placing the anode outside of the heart

Methods and materials

Right ventricular pacing was accomplished in 20 patients by use of a transvenous pacing catheter inserted percutaneously into an antecubital vein (8 patients) or a femoral vein (12 patients) The catheter was advanced to the right ventricle using either radiographic or electrocardiographic monitoring[8] Although we propose a two electrode catheter (anode remote) for general use for the purposes of this study the catheters used were 4 French 110 cm. long with one electrode (distal) 2 mm wide at distal tip one electrode (proximal) 2 mm wide 1 cm from the distal tip and one electrode (remote) 5 mm wide 23 cm from the distal tip * Three terminals at the proximal end of the catheter (positioned outside of the body) are connected to the three electrodes (Fig 1) When the distal and proximal electrodes are connected to the pacemaker pulse generator the catheter acts as a bipolar electrode system similar to bipolar temporary pacing catheters in common use When the distal and remote electrodes are connected to the pulse generator the catheter acts as a unipolar electrode system The remote electrode is larger so as to avoid excitation of the surrounding tissue In this study when using the unipolar electrode configuration the distal electrode was always connected to the cathode (−) of the pulse gererator and the remote electrode was always connected to the anode (+) of the pulse generator

The three electrode catheter was designed to compare bipolar with unipolar pacing in the same patient without changing the catheter or the position of the catheter For each patient after positioning the catheter tip in the right ventricle the pacing stimulation threshold (ma) and the interelectrode electrogram of unpaced beats (mV) were measured in both the bipolar (distal proximal) and unipolar (distal remote) electrode configurations Peak voltage was meas

From the University of Washington School of Medicine and the Division of Cardiology Harborview Medical Center Seattle

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Reprint requests. Dr Thomas A Preston Harborview Medical Center 325 Ninth Ave Seattle Wash 98104

*Made by Electro Catheter Corporation Rahway N J

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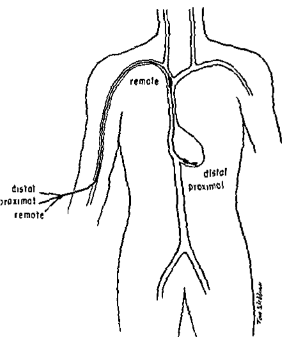


Fig 1 A Test catheter inserted into a right ventricle through an antecubital vein. The remote electrode is 23 cm proximal to the distal tip outside the heart

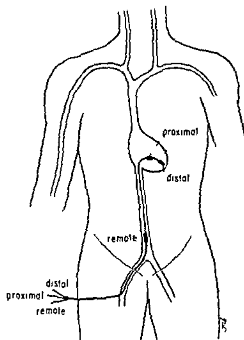


Fig 1 B Test catheter inserted through right femoral vein.

the heart and the other outside the heart but within the body gives a significantly (P < 0 02) greater signal for demand pacemaker sensing *As most external pacemakers require a 2 to 3 mV signal for proper sensing in the demand mode signals of amplitude less than 3 mV often are not* sensed Furthermore with any bipolar electrode configuration an ectopic or conducted beat with a mean vector perpendicular to the axis between the two intracardiac electrodes may produce a signal smaller than that required for sensing [3 7 9] For example the ventricular ectopic beats of Patient F E produced low amplitude signals as seen by the bipolar electrodes and were not sensed by the pacemaker Thus for a bipolar electrode system it is possible to have ventricular depolarizations which are not sensed, resulting in competition between the artificial pacemaker and spontaneous beats Patients with acute myocardial infarction especially can have very low signals as sensed by a bipolar system [9] A unipolar electrode system however not only gives greater signals but there is very little variation in the amplitude of the unipolar signal sensed from beats of different origin

Unipolar pacing catheters with a single electrode inside the body were the first type introduced for temporary pacing [10] but were abandoned largely because of the inconvenience and unreliability of suturing or attaching the indifferent electrode (anode) on or under the skin [11 12] Initially it was thought that bipolar electrodes were more reliable because it was not necessary that the electrodes be in contact with the endocardial surface [11] but subsequent studies on unipolar vs bipolar thresholds showed no significant difference between the two systems [13] Earlier studies showing lower thresholds for the bipolar electrodes may have resulted from smaller electrode surface areas used for the newer bipolar electrodes [12] Parsonnet and co workers[14] later suggested that unipolar thresholds may be lower than bipolar thresholds In the study reported in this paper the distal electrode (cathode) was the same for unipolar or bipolar pacing and there was no discernible difference in threshold between the two electrode configurations There is still the possibility that a poorly positioned unipolar catheter which is not in contact with the endocardium may have wide swings in threshold and, therefore inconsistent pacing In our study more than half (11 out of 20) of the catheters were inserted without fluoroscopy with less than optimal catheter position In only one instance

Table I Sensed signal (mV)

Patient	Vein	*Normally conducted beats*		*Ventricular ectopic beats*		*Threshold (ma.)*	
		Bipolar	*Unipolar*	*Bipolar*	*Unipolar*	*Bipolar*	*Unipolar*
I S	F	–	–	4 2	6 4	0 8	0 8
J H	A	–	–	6 0	5 0	1 3	1 3
P F	F	1 7	6 2	–	–	0 3	0 3
T J	A	2 2	8 8	–	–	4 0	4 0
J W	F	12 0	7 0	4 8	10 0	0 2	0 2
R H	A	3 6	5 8	–	–	0 5	0 5
F E	A	4 0	8 2	2 4	7 0	0 5	0 5
R D	F	8 0	12 0	5 5	12 0	0 6	0 6
V M	F	–	–	2 6	3 7	0 4	0 4
I I	F	–	–	3 4	5 8	0 3	0 3
F W	F	4 3	6 3	–	–	0 3	1 0
A L	F	4 0	7 5	–	–	3 0	3 0
D S	F	3 8	3 8	–	–	0 7	0 6
K E	A	–	–	7 0	8 3	0 8	0 8
F S	A	3 9	5 6	–	–	0 5	0 5
D S	F	3 0	5 2	–	–	0 5	0 5
J C	F	1 4	3 9	–	–	0 9	0 9
J K	A	–	–	5 0	9 3	0 5	0 5
G N	F	1 5	6 2	2 4	6 6	2 0	2 0
E A	A	–	–	4 8	6 8	1 0	1 0
	Mean	4 1 ± 2 9	6 7 ± 2 2	4 4 ± 1 5	7 4 ± 2 4		
		P < 0 02		P < 0 003			

Abbreviations mV millivolts ma milliamps F femoral A antecubital Bipolar sensing between distal and proximal electrodes Unipolar sensing between distal and remote electrodes
Not sensed by demand pacemaker

ured from baseline to maximum deflection using a Hewlett Packard 1500A Electrocardiograph or an Electronics for Medicine VR 6 recorder If more than one type of spontaneous ventricular depolarization occurred (ventricular ectopic beats, aberrantly conducted beats or normally conducted beats) the voltage sensed on both configurations was recorded

Results

Interelectrode potentials were measured in all patients using both bipolar and unipolar electrode connections (Table I) The mean sensed potential of regularly conducted beats was 6 7 mV for the unipolar and 4 1 mV for the bipolar configuration (P <0 02) and for the ectopic ventricular beats it was 7 4 mV for the unipolar and 4 4 mV for the bipolar electrode configuration (P <0 003) Using unipolar electrodes, in every instance except two (J H and J W), the voltage sensed exceeded or equaled that sensed with bipolar pacing Furthermore although it was not uncommon to have a bipolar potential of less than 3 mV (6 out of 20), in no case was the unipolar sensed signal less than 3 7 mV and in all but three instances the unipolar potential exceeded 5 mV In three patients ventricular ectopic beats were not sensed in the bipolar configuration but were sensed in the unipolar configuration (Fig 2)

The threshold for ventricular stimulation was the same for unipolar as for bipolar pacing in all instances except two (F W and D S) All patients denied body twitching or discomfort while being paced in the unipolar mode (anode outside of the heart but inside of the body)

Discussion

The use of a unipolar pacing catheter has two advantages over conventional bipolar temporary pacing catheters (1) consistently greater detected voltage of any type of ventricular depolarization sensed through the electrode system and (2) less chance of pacemaker induced ventricular arrhythmia if a pacemaker stimulus falls during the vulnerable period of the preceding ventricular depolarization

The results of this study show that a unipolar electrode configuration with one electrode inside

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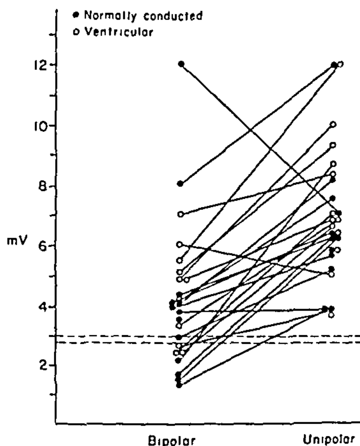


Fig 2 Comparison of signals sensed by bipolar and unipolar electrode systems using the same catheter in the same position in the right ventricle The dotted lines mark the level below which most external pacemakers do not sense mV = millivolts

was catheter repositioning necessary, the catheter had been inserted without fluoroscopy and subsequently displaced to outside the right ventricle There was no indication of difference of pacing stability between the two electrode configurations

It is probable that by spacing the two electrodes 8 to 10 cm apart a maximal signal can be detected But as the proximal electrode must be used for pacing as well as sensing an electrode 8 to 10 cm from the distal tip might pace the right atrium or sense atrial depolarizations so it is well to remove the proximal electrode to outside the heart With the anode 23 cm proximal to the distal tip when the distal electrode is in the right ventricle the anode is always outside the heart but within the body whether the femoral antecubital or subclavian vein is used for insertion of the catheter Widely spaced electrodes should be more susceptible than bipolar electrodes to electromagnetic interference, but placing the indifferent electrode in the superior vena cava or inferior vena cava affords much more protection from interference than if the indifferent electrode (anode) is on or just beneath the skin. In this study there was no detectable interference and no vulnerability to skeletal muscle potentials

Despite improved sensing with a unipolar electrode system it is still possible that the sensing mechanism of a pacemaker may not function properly and sometimes only fixed rate (competitive) pacing is available Pacemaker induced ventricular arrhythmias may be very uncommon but the patients at highest risk for this complication are precisely those in whom temporary pacing is often necessary, i e patients with myocardial infarction hypoxia or metabolic imbalance Although the evidence is not conclusive it does seem likely that *pacemaker induced excitation during the vulnerable period occurs much more commonly with anodal stimulation than with cathodal stimulation.*[6] The electrophysiologic explanation is that during the relative refractory period (containing the vulnerable period) there is commonly an interval during which threshold of excitation (a single propagated depolarization) is much lower at the anode than at the cathode[15] Since ventricular fibrillation can result from a single depolarization during the vulnerable period it follows that induction of ventricular fibrillation is more likely at the anode Furman and Mehra[16] have obtained data from dog experiments corroborating this premise

Removing the anode from within the heart should lessen the likelihood of inducing a ventricular arrhythmia by pacing during the vulnerable period The large surface area of the remote electrode also prevents excitation of tissue contiguous to it It is very important that the distal tip electrode be the cathode and the remote electrode the anode so as to lower the threshold of diastolic excitation (lower at cathode) but raise the threshold of fibrillation (lower at anode)

In summary, a unipolar catheter (cathode at distal tip anode 23 cm back) for temporary pacing provides two advantages over bipolar catheters increased signal detection which allows better noncompetitive pacer function and decreased risk of pacer induced ventricular arrhythmia if the pacemaker operates in the competitive mode For patients undergoing temporary pacing a unipolar electrode system is safer than a bipolar system

ventricular measurements were obtained by the insertion of an indwelling nylon catheter (I D 1 0 mm O D 1 4 mm) into the femoral artery by the Seldinger technique [11] Because of the non opaque nature of this latter catheter it was ad vanced into the left ventricular cavity with a guide wire in place

After positioning the venous and arterial cath eters respectively in the pulmonary artery and aorta the patient relaxed for 15 minutes in order to return to a steady state prior to blood sam pling and pressure measurements At the end of this period, 10 ml samples of mixed venous and arterial blood were drawn into heparinized syringes using proper anaerobic technique The blood samples were iced and taken immediately to the laboratory and analyzed for oxygen saturation and tension and hemoglobin con centration Then pressures of the pulmonary ar tery right ventricle and right atrium were recorded in rapid succession Subsequently the arterial catheter was advanced to the left ventri cle and pressures in this cavity and in the aorta were also recorded in close succession

Pressures were measured by means of a P23Db Statham strain gauge and a Phillips elec tromanometer and recorded in a Cardiopan 573 heat stylus recorder simultaneously with Lead II of the electrocardiogram The sensitivities used were as follows 2 5 1 2 0 62 and 0 31 mm of deflexion per millimeter of mercury Zero ref erence point was 10 cm. below the sternal angle as determined with a carpenter s spirit level The recorder paper speeds employed were 10 25 and 50 mm per second Mean pressures were always recorded at 10 mm per second while diastolic ventricular pressures were recorded at 50 mm per second

Mean pressures were measured by electronic integration The values for systolic and diastolic pressures represent the arithmetic mean of ten measurements Diastolic ventricular pressures were measured at the initial (D_1) and *final* (D_2) diastole and at the plateau this latter also being measured at the right atrial pulse tracing D_1 *cor* responds to the lowest point reached by the pulse tracing in initial diastole and D_2 to the point *prior* to the upswing of systolic pressure When pres ent the plateau represents the mean value of points taken between the *peak of* the pressure rise which suddenly follows D_1 and the point im mediately prior the inscription of the a wave in patients with a normal sinus rhythm, and at D_2 in patients with atrial fibrillation The number of points taken were variable depending on the swinging up and down of this segment of the pulse tracing

Oxygen tension determinations were per formed with the Clark electrode connected to a Radiometer pH meter (PHM 27) with a gas moni tor (PHA 927) Oxyhemoglobin saturations were measured in an A0 oximeter model No 108000 Hemoglobin concentrations were determined by the cyanomethemoglobin method [6]

The cardiac output was calculated by the Fick principle The assumed oxygen consumption was based on age sex and heart rate as recom mended by LaFarge and Miettinen [12] From the oxygen tension saturation and hemoglobin con centration the arterial and venous oxygen con tent were calculated.

The pulmonary arteriolar resistance was calculated by the following formula

$$PAR\ (dynes/sec/cm^{5}) = \frac{PA\ (mm.\ Hg) - LVed\ (mm\ Hg) \times 60 \times 1330}{CI\ (ml/min/M)}$$

where PA = pulmonary artery mean pressure LVed = left ventricular end diastolic pressure *CI* = cardiac index

Control values for pressures arteriovenous ox ygen content difference and pulmonary arterio lar resistance were obtained in 22 individuals ten with minor surgical problems and 12 who have had cardiac catheterization performed because of the presence of heart murmurs Their ages ranged from 10 to 49 years (mean = 23 9) Thirteen patients were males and nine patients were females The control mean values plus or minus two times the correspondent standard deviation ($\overline{X} \pm 2$ S D) were taken as the upper and lower limits of normal for each one of the pa rameters under consideration

Results

Control values for right and left side heart pressures for the ratio between the end diastolic and systolic pressures in both ventricles cardiac output and pulmonary arteriolar resistance are presented in Table II

Table III shows the individual values for the ratio between the end diastolic and systolic pressures *(D/S)* in both ventricles of patients

Hemodynamics in endomyocardial fibrosis

Armênio C Guimarães, M D
Ademar Santos Filho M D *
Jose Pericles Esteves M D
Lucia S A Vinhaes M D
Waldeck Neves Abreu M D
Bahia, Brazil

Endomyocardial fibrosis, a myocardiopathy of unknown etiology is highly prevalent in Uganda and Nigeria but several cases have been reported from other parts of Africa, Asia and South America and occasional cases from North America and Europe [2,3,13,16] Pathologically it is characterized by fibrous thickening of the mural endocardium involving preferentially the inflow tract of one, or more commonly, both ventricles [7] Very frequently the papillary muscles and chordae tendinae are also involved by the fibrous process leading to atrioventricular regurgitation [7,10,13] Clinically the most prominent features of patients with biventricular or only right ventricular disease are massive severe ascites and neck vein distention[10,13,14] in patients with isolated left ventricular disease signs of mitral insufficiency and/or of pulmonary hypertension predominate [9,14]

From the hemodynamic point of view right ventricular involvement is characterized by a restrictive pattern of the pressure curves in the right sided heart cavities [8,14,15] while left ventricular disease has been assessed indirectly, by the alterations of the pulmonary capillary pressure curve [14] The cardiac output has also been measured by some authors,[15] but the results have been influenced by the presence of significant anemia in the majority of these patients In addition, due to technical difficulties the mixed venous blood has been sampled at the right atrial level These facts, certainly have limited the comprehension of the hemodynamic picture in this condition

The present report presents the analysis of the hemodynamic studies in patients with endomyocardial fibrosis as seen in Bahia Brazil

Subjects and methods

Nine patients with endomyocardial fibrosis were studied between August 1970 and December 1972 The main clinical findings are presented in Table I Their age ranged from 12 to 54 years averaging 32 4 years Seven patients were females and two patients were males The clinical diagnosis was confirmed in each individual by right ventricular angiography Two of these patients eventually died and in one instance the clinical diagnosis was confirmed at autopsy The other patient died outside the Hospital and no autopsy was obtained The criteria for clinical angiocardiographic and anatomic diagnosis of endomyocardial fibrosis have been well described by other investigators [4,7,13] and our own experience has been reported in detail elsewhere [10]

Patients were submitted to right and left heart catheterization in a fasting state and received 10 mg of Diazepam orally 30 minutes before the procedure They remained supine on a horizontal x ray table throughout the procedure In those patients who presented with severe ascites an adequate paracentesis was performed the day before the study to insure the patient s comfort in this position

Right heart catheterization was performed via a 6F or 7F Cournand catheter while left

From the Department of Medicine and Hospital Prof Edgard Santos University of Bahia Medical School Salvador Bahia Brazil
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Reprint requests to Dr Armenio C Guimaraes Hospital Prof Edgard Santos Salvador 40000 Bahia Brazil
Dr Ademar Santos Filho is a Research Assistant from the Conselho Nacional de Pesquisas

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Ascites	Hepato megaly	Spleno megaly	Peripheral edema	Cyanosis
+	+	+	–	–
+	+	–	+	+
+	+	–	+	–
+	+	–	–	+
+	+	–	–	+
+	+	+	–	–
+	+	–	+	–
+	+	+	–	–
+	+	+	+	+

nd systolic ventricular pressures and for the
dgard Santos Bahia Brazil 1973

LV		Ao		
S	D_2	S	D	Mean
98 9-42 3	6 7 11 9	98 0 142 3	62 5 85 8	78 8 114 8
115 3	8 8	113 4	74 6	95 0
11 8	1 6	12 2	7 1	10 3
138 9	12 0	137 8	88 8	115 6
91 7	5 6	89 0	60 4	74 4

Pulmonary arteriolar resistance (dynes/sec/cm⁻⁵)
37 2 297 1
109 0
55 9
220 8

SD = standard deviation.

gradients between the diastolic pulmonary artery pressure and, respectively the plateau and end diastolic right ventricular pressures and between the left ventricular end diastolic and right atrial mean pressures are shown in Table V

Group I Seven patients were classified in this group As Table III shows except for Patient No 7 the D_2/S ratio for the right ventricle is above 60 per cent. Only Patient No 2 presents severe elevation of this ratio for the left ventricle (128 6 per cent above its upper control limit) while the other patients show a mild to moderate increase or a normal value as in Patients No 8 and 9

Six patients in this group present a restrictive pattern of the dip and plateau type for the right atrial pressure curve (Table IV and Fig 1 *A*) The right atrial mean pressure shows severe elevation (equal or above 20 mm Hg) in four patients two of them with atrial fibrillation (Table IV) This arrhythmia is however also present in two other patients (Nos 7 and 9) with respectively moderate and slight elevation of this pressure

The amplitude of the a wave is markedly elevated (above 19 mm Hg) in the three patients with a normal sinus rhythm (Nos 5 6 and 8) being close to peak right ventricular systolic pressure in Patients Nos 5 and 6 and slightly above it in Patient No 8 (Table IV)

Except for patients Nos 7 and 8 evidence suggestive of severe tricuspid regurgitation is present in all the patients in this group Indeed, the amplitude of the v wave is close to the peak systolic right ventricular pressure being even equal in Patient No 2 (Table IV) In addition in Patients Nos. 5 and 6 in normal sinus rhythm the value of the x descent is marked above that for the y descent.

All the patients in this group present a dip and plateau pattern for the right ventricular pressure curve (Table IV and Figs 1 *A* and *B*) The end diastolic pressure in this ventricle is more than twice its upper control limit (8 6 mm Hg Table II) in 4 patients (Nos 2 4 5 and 6) The peak systolic pressure is in the control range (Tables II and IV) except for Patient No 9 who presents a low value (12 1 mm. Hg) In more advanced cases as evidenced by a D_2/S ratio for the right ventricle above 60 per cent the contour of the right ventricular pulse pressure becomes completely distorted and very similar to the contour of the right atrial pulse (Figs 1 *A* and *B*)

The mean pulmonary arterial pressure shows mild elevation in all but Patients Nos 8 and 9 who present a normal value (Table IV) The pulmonary arteriolar resistance is normal in two patients and mildly elevated in the other five patients

As revealed by the pressure gradients presented in Table V the diastolic pressure in the pulmonary artery is slightly lower than the right

Table I Main clinical findings in nine patients with endomyocardial fibrosis Hospital Professor Edgard

Patient No	Age (yr)	Sex	Race	Dyspnea on exertion	Pulse rate	Blood pressure	Loud pulmonic component of the second sound	Mitral regurgitant murmur*	Tricuspid regurgitant murmur*	Distended neck ve s
1	38	F	Mulatto	+	92	95/70	+	+++	+	+
26†	34	M	Mulatto	+	100	90/60	+	++	–	+
3	15	F	Negro	+	108	115/75	+	++	–	+
4	36	F	Mulatto	–	80	100/60	–	++++	–	+
5	36	F	Mulatto	+	100	100/80	–	+++	–	+
6	28	F	Caucasian	+	62	90/60	+	++	+++	+
7‡	54	F	Mulatto	–	74	100/70	+	++	–	+
8	12	F	Mulatto	+	105	90/60	–	–	–	+
9†	39	M	Mulatto	+	94	100/80	–	–	–	+

Murmurs graded from + to ++++++ [5]
†Patients with large chronic pericardial effusion
‡Patient who had necropsy

Table II Control values for cardiac pressures for the cardiac index for the ratio between the end diastolic ... pulmonary arteriolar resistance obtained in 22 patients without cardiopulmonary disease Hospital Profess...

	Pressures (mm. Hg)									
	RA					RV		PA		
	Mean	a	x	v	y	S	D_2	S	D	Mean
Range	0 4 6 9	2 7 10 0	2 4 5 6	1 0 7 5	0 4 5 5	15 4 33 0	1 1 7 9	11 4 26 4	4 2 13 3	8 1 17 9
Mean	4 2	6 3	2 1	4 8	3 2	25 2	4 6	20 1	8 9	14 2
S D	1 6	1 5	1 8	1 6	1 4	5 3	2 0	4 4	2 4	2 8
Mean ±2 S D	7 4	9 3	5 7	8 0	6 0	31 8	8 6	28 9	13 7	19 8
	1 0	3 3	–1 5	1 6	0 4	14 6	0 6	11 3	4 1	8 6

	D_2/S (%)		Cardiac index (L /min./M²)
	RV	LV	
Range	5 0 28 6	5 3 9 8	2 6 5 2
Mean	18 3	7 4	3 9
S D	7 0	1 2	0 97
Mean ±2 S D	32 3	9 8	5 84
	4 3	5 0	1 96

Abbreviations RA – right atrium RV – right ventricle PA – pulmonary artery LV – left ventricle Ao aorta D_2 – end diastolic ventricular pressure

with endomyocardial fibrosis This ratio has been intended as a measure of the degree of hemodynamic disturbance imposed by the endocardial thickening It was used previously for the same purpose by Yu and co workers[17] in patients with constrictive pericarditis In parentheses in Table III are the values for the percentage increase of this ratio above its upper control limit for each ventricle Based upon this patients were divided in two groups as follows Group I, predominant or isolated right ventricular disease and Group II, predominant left ventricular disease

Individual values for pressures arterious venous oxygen content differences oxygen consumption cardiac index and pulmonary arteriolar resistance in each one of these two groups are presented in Table IV Individual values for the

40
0
PA
RV
RA
20
0
PA
RV
RA

Fig 1 Pressures (in millimeters of Hg) in two patients with endomyocardial fibrosis *Top* Patient No 5 *Bottom*, *Patient* No 8 *In both* patients right ventricular and right atrial pressure contour are very similar Observe the characteristic early dip and plateau pattern of the right atrial and ventricular pressures in Patient No 5 In Patient No 8 the amplitude of the a wave is slightly above the peak right ventricular systolic pressure and the steep rise of pressure in the pulmonary artery occurs between the inscription of the P wave and QRS complex in the electrocardiogram



Fig 2. Left ventricular diastolic pressure (in millimeters of Hg) in a patient with biventricular endomyocardial fibrosis (Patient No 1) Observe the early dip-and plateau *pattern*.

Table III Values for the ratio between the end diastolic and systolic pressures (D_2/S) in the right and left ventricles of nine patients with endomyocardial fibrosis*†

Group	Patient no	D_2/S (%)	
		RV	LV
I	2	82 7 (156 0)	22 4 (128 6)
	4	77 7 (140 6)	13 3 (10 8)
	5	75 9 (135 0)	13 7 (12 1)
	6	86 0 (166 3)	11 3 (4 6)
	7	46 2 (43 0)	10 6 (2 5)
	8	61 8 (91 3)	5 5
	9	64 4 (99 4)	9 5
II	1	36 1 (11 8)	20 1 (105 1)
	3	55 1 (70 6)	22 2 (126 5)

Abbreviations identical to Table II

†Patients grouped according to the predominant value for the percentage increase of D_2/S ratio above its upper control limit (numbers inside parentheses) Further explanations in text.

ventricular plateau pressure in four patients (Nos 2 5 8 and 9) and than the right ventricular end diastolic pressure in five patients (Nos 2 4 5 6 and 9) In all these patients, except for Patient No 7, the contour of the pulmonary artery pressure curve documents that the rise in pressure inside this artery occurs before the onset of right ventricular systole as illustrated in Figs 1 *A* and *B* In Fig 1 *A* the rise of pressure inside the pulmonary artery is related to the initial part of the right ventricular plateau pressure while in Fig 1 *B* it occurs between the inscription of the P wave and the onset of the QRS complex in the simultaneous electrocardiographic lead recorded corresponding with a delay of 0 11 second to the inscription of a very tall a wave in the right atrial pulse As illustrated in Fig 1 and documented in Table IV in patients of this group with a normal sinus rhythm the amplitude of this atrial wave is close to the peak systolic pulmonary artery pressure

Except for Patients Nos 5 and 8 all patients in this group also present a restrictive pattern of the dip and plateau type for the left ventricular pulse pressure curve (Fig 2) The D_2/S ratio shows a normal value in Patients Nos 8 and 9 severe elevation in Patient No 2 (the highest value for both groups of patients), and mildly elevated values in the other five patients (Table III) The gradient between the left ventricular end diastolic and right atrial mean pressure is reverted in all but Patient No 9 (Table V)

Sytemic pressures are in the normal range. The cardiac index is below the average control value in all patients being abnormally low in three of them (Nos 4, 5 and 7, Table IV)

Group II There are two patients in this group (Nos 1 and 3) In Patient No 1 the D_2/S ratio for the right ventricle is only slightly elevated suggesting mild right ventricular disease while the value of this ratio for the left ventricle is one of the highest observed (20 1 per cent, Table III) The pulse pressure contour is this latter cavity shows an early dip followed by a plateau (Fig 2) The mean pulmonary artery pressure is only mildly elevated while the pulmonary arteriolar resistance is normal (Table IV)

Patient No 3 shows evidence of severe biventricular disease with high values of the D_2/S ratio for both ventricles (Table III) The contour of the pulse pressure in the right atrium and right ventricle is of the dip and plateau type and the mean right atrial pressure is the highest among the patients studied (28 mm Hg Table IV) However there are no hemodynamic evidences of tricuspid regurgitation The pulmonary artery mean pressure and arteriolar resistance show respectively, moderate and mild elevation (Table IV) The left ventricular end diastolic pressure is severely elevated (30 2 mm Hg Table IV) but the pulse pressure contour in the ventricles does not exhibit the early dip and plateau

In both these patients the gradients presented in Table V are not reverted The absence of a dip and plateau pattern for the right ventricular pulse pressure in Patient No 1 avoids the calculation of the gradient between the mean pulmonary artery and the right ventricular plateau pressure

The values for systemic pressures and cardiac index are normal (Table IV)

Discussion

1 The majority of the patients under study present hemodynamic evidence of biventricular endomyocardial fibrosis with predominant right ventricular disease findings which are in accord with the frequency distribution of the type and degree of ventricular involvement in this cardiopathy [7,13] Except for Patient No 7 in Group I and Patient No 1 in Group II all the patien

Fig 1 Pressures (in millimeters of Hg) in two patients with endomyocardial fibrosis *Top* Patient No 5 *Bottom,* Patient No 8 *In both patients right ventricular and right atrial pressure contour are very similar* Observe the characteristic early dip and plateau pattern of the right atrial and ventricular pressures in Patient No 5 In Patient No 8 the amplitude of the a wave is slightly above the peak right ventricular systolic pressure and the steep rise of pressure in the pulmonary artery occurs between the inscription of the P wave and QRS complex in the electrocardiogram

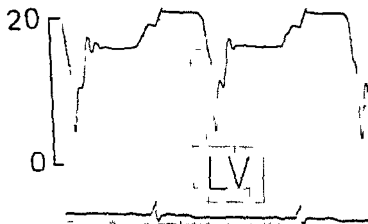


Fig 2 Left ventricular diastolic pressure (in millimeters of Hg) in a patient with biventricular endomyocardial fibrosis (Patient No 1) Observe the early dip-and plateau pattern.

Table IV Values for right and left cardiac pressures, the arteriovenous oxygen content difference, oxygen
lar resistance obtained in nine patients with endomyocardial fibrosis * Hospital Prof Edgard Santos

Groups	Patient No	Pressures (mm. Hg) RA Mean	Plateau	a	x	v	y	RV S	D_1
I	2	24 0	22 7	–	22 0	28 6	18 2	28 3	19 0
	4	22 0	21 6	–	21 3	26 4	16 3	25 6	12 0
	5	21 5	22 9	23 8	20 0	25 2	14 6	27 4	12 6
	6	20 0	17 7	20 7	20 5	22 6	16 3	23 0	17 6
	7	16 8	14 3	–	16 2	20 0	10 6	32 0	9 8
	8	13 8	–	19 8	9 4	15 0	10 5	19 4	9 8
	9	8 0	7 8	–	6 8	10 0	5 0	12 1	3 3
II	1	9 0	–	12 8	6 0	11 2	5 6	30 8	2 3
	3	28 0	30 0	30 1	22 3	27 6	25 1	50 5	21 7

Groups	Patient No	Pressures (mm. Hg) LV D_1	Plateau	D_2	S	A_0 S	D	Mean	A V (ml/100 ml)
I	2	12 6	19 7	20 9	93 1	91 2	68 8	80 0	5 27
	4	3 4	16 5	17 2	129 4	126 8	76 3	66 0	7 30
	5	1 8	–	14 8	107 8	107 8	82 1	97 6	6 92
	6	0 1	9 2	11 0	97 0	92 1	60 0	76 6	4 92
	7	8 0	10 8	11 2	105 6	102 4	63 0	80 0	5 63
	8	1 4	–	6 0	103 8	103 7	80 0	92 8	6 41
	9	4 0	9 8	10 0	104 6	102 3	63 3	86 7	6 19
II	1	-1 3	14 4	19 0	94 4	92 0	64 7	76 3	3 43
	3	10 0	–	30 2	136 0	132 8	87 9	99 8	5 60

D_1 = initial diastolic ventricular pressure A V = arteriovenous oxygen content difference MVO_2 = oxygen consumption CI = cardiac index other ab-

presented a D /S ratio for the right ventricle above 50 per cent indicating the severity of involvement of this chamber (Table III)

In patients with such advanced right ventricular disease the contour of the right atrial and/or ventricular pulse pressure shows an early dip followed by a plateau, characterizing the restrictive obliterative nature of this cardiopathy [8,13,15] At this stage the right atrial mean pressure is usually very high The mildly to moderately elevated values observed in Patients Nos 8 and 9 (Group I, Table IV), both with very high right ventricular D_2/S ratios, may have been secondary to the use of diuretics and to the removal of ascitic fluid which preceded the study [1] In this regard, the findings of other investigators have shown that, in this condition, the highest levels of right atrial mean pressure have been present with chronic atrial fibrillation [8,15]

2 Severe tricuspid regurgitation seems to constitute a very common complication of predominant right ventricular endomyocardial fibrosis, being present in six out of seven patients in Group I This finding represents the hemodynamic counterpart of the pathologic involvement of the tricuspid valve in this condition [7,13] The severity of this type of tricuspid regurgitation is suggested by the similarity of the contour and amplitude of the right atrial and ventricular pulse pressures both chambers thus function as a single cavity throughout the cardiac cycle (Fig 1 A)

3 Group I patients present evidence of a very interesting mechanism of circulatory adjustment, which has also been pointed out by other investigators [6,14] As indicated in Table V five patients in this group have a right ventricular end diastolic pressure slightly higher than the

consumption cardiac index and pulmonary arterio
Bahia Brazil 1973

		IA		
Plateau	D_2	*S*	*D*	*Mean*
22 6	23 4	28 0	20 0	24 0
19 6	19 8	25 0	19 7	23 2
22 6	20 8	25 7	16.3	20 0
18 0	20 7	22 9	18 2	20 4
14 6	14 8	31 0	14 8	20 4
14 0	12 0	18 6	13 3	15 0
8 2	7 8	12 3	7 6	10 4
—	10 4	28 6	12 1	21 2
27.8	27 8	56 1	31 2	41 6

MVO_2 (ml/min/M²)	CI (L/Min/M²)	PAR (Dynes/sec/cm⁻⁵)
124 9	2 37	104 4
109 0	1 50	319 2
109 0	1 57	264 3
102 2	2 07	36? 4
108 2	1 92	382 4
133 0	2 07	347 0
125.2	2 12	15 1
109 0	3 17	5? 4
132 0	2 35	387 1

breviations simila to those of Table I

diastolic pulmonary artery pressure and in four of them this latter pressure is also lower than the right ventricular plateau pressure These findings are consistent with an early opening of the pulmonic valve occurring in mid or end diastole as illustrated in Figs 1 A and B If in addition we consider that all Group I patients except No 9 have a right atrial mean pressure higher than the left ventricular end diastolic pressure (Table V) we may postulate that in these patients there are hemodynamic conditions favoring a diastolic blood flow from the right atrium to the left ventricle The effective contribution of this flow to left ventricular filling and its consequent influence in left ventricular stroke volume remains to be evaluated. However if we consider that only two of the six patients presenting evidences suggestive of this mechanism have a subnormal cardiac output, we may suppose that it contributes effectively to the maintenance of the circulation It should be emphasized that the values for cardiac output did not show any difference regarding the presence of normal sinus rhythm or atrial fibrillation (Table IV) suggesting that once the gradient favoring a proper diastolic pulmonary flow is established the contribution of atrial contraction is not of paramount importance for the hemodynamic equilibrium of these patients.

4 As the right ventricular disease becomes more severe the right ventricular pressure contour tends to become more distorted[8,14,15] (Figs 1 A and B) The basic reason for this distortion is the progressive elevation of the end diastolic ventricular pressure without a proportional increase of the peak systolic pressure as has been expressed quantitatively by the very high D_2/S right ventricular ratio obtained in these patients. Ratios showing an increase of more than 100 per cent above its upper control limit occurred only in Group I patients who present a reversal of the gradient between the left ventricular end diastolic and the mean right atrial pressures consistent with a diastolic pulmonary blood flow, as discussed (Tables III and V) This fact suggests that, in addition to the decreased ventricular distensibility the early opening of the pulmonic valve seems to constitute an important factor in the genesis of this narrow ventricular pulse pressure Both these factors tend to decrease the end diastolic right ventricular myocardial fiber length probably weakening the right ventricular contraction force

In patients with a normal sinus rhythm the transmission of a very potent atrial contraction reaching the same amplitude as the peak ventricular systolic pressure (Fig 1 B) also contributes to the distorted appearance of the ventricular pressure curve

The majority of patients with an elevated D_2/S ratio for the left ventricle exhibited a dip and plateau type of pressure contour (Fig 2) However this morphology may be absent, even in the presence of severe elevation of the end diastolic pressure as illustrated by Patient No 3 (Group II Table IV) The explanation for this finding may reside in the different locations in which the left ventricular endocardial thickening may occur in this condition sometimes involving the mitral valve alone or predominantly[13] In this situation the hemodynamic disturbance will

Table IV Values for right and left cardiac pressures the arteriovenous oxygen content difference oxygen lar resistance obtained in nine patients with endomyocardial fibrosis * Hospital Prof Edgard Santos

		Pressures (mm Hg)							
		RA						*RV*	
Groups	*Patient No*	*Mean*	*Plateau*	*a*	*x*	*v*	*y*	*S*	D_1
I	2	24 0	22 7	—	22 0	28 6	18 2	28 3	19 0
	4	22 0	21 6	—	21 3	26 4	16 3	25 6	12 0
	5	21 5	22 9	23 8	20 0	25 2	14 6	27 4	12 6
	6	20 0	17 7	20 7	20 5	22 6	16 3	23 0	17 6
	7	16 8	14 3	—	16 2	20 0	10 6	32 0	9 8
	8	13 8	—	19 8	9 4	15 0	10 5	19 4	9 8
	9	8 0	7 8	—	6 8	10 0	5 0	12 1	3 3
II	1	9 0	—	12 8	6 0	11 2	5 6	30 8	2 3
	3	*28 0*	*30 0*	*30 1*	*22 3*	*27 6*	*25 1*	*50 5*	*21 7*

		Pressures (mm Hg)							
		LV				A_0			
Groups	*Patient No*	D_1	*Plateau*	D_2	*S*	*S*	*D*	*Mean*	*A V (ml/100 ml)*
I	2	12 6	19 7	20 9	93 1	91 2	68 8	80 0	5 27
	4	3 4	16 5	17 2	129 4	126 8	76 3	86 0	7 30
	5	1 8	—	14 8	107 8	107 8	82 1	97 8	6 92
	6	0 1	9 2	11 0	97 0	92 1	60 0	76 6	4 92
	7	8 0	10 8	11 2	105 6	102 4	63 0	80 0	5 63
	8	1 4	—	6 0	108 8	103 7	80 0	92 8	6 41
	9	4 0	9 8	10 0	104 6	102 3	68 3	86 7	6 19
II	1	−1 3	14 4	19 0	94 4	92 0	64 7	76 3	3 43
	3	10 0	—	30 2	136 0	*132 8*	*87 9*	*99 8*	5 60

D_1 = initial diastolic ventricular pressure A V = arteriovenous oxygen content difference MVO_2 = oxygen consumption CI = cardiac index other ab

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In patients with such advanced right ventricular disease, the contour of the right atrial and/or ventricular pulse pressure shows an early dip followed by a plateau characterizing the restrictive obliterative nature of this cardiopathy [8 13 15] At this stage the right atrial mean pressure is usually very high The mildly to moderately elevated values observed in Patients Nos 8 and 9 (Group I, Table IV) both with very high right ventricular D_2/S ratios may have been secondary *to* the use of diuretics and to the removal of ascitic fluid which preceded the study [1] In this regard, the findings of other investigators have shown *that, in* this condition the highest levels of right atrial mean pressure have been present with chronic atrial fibrillation [8 15]

2 Severe tricuspid regurgitation seems to con*stitute a very common complication of predomi*nant right ventricular endomyocardial fibrosis being present in six out of seven patients in Group I This finding represents the hemodynamic counterpart of the pathologic involvement of the tricuspid valve in this condition [7 13] The severity of this type of tricuspid regurgitation is suggested by the similarity of the contour and amplitude of the right atrial and ventricular pulse pressures both chambers thus function as a single cavity throughout the cardiac cycle (Fig 1 *A*)

3 Group I patients present evidence of a very interesting mechanism of circulatory adjustment which has also been pointed out by other investigators [8 14] As indicated in Table V five patients in this group have a right ventricular end diastolic pressure slightly higher than the

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Table V Pressure gradients in nine patients with *endomyocardial fibrosis* Hospital Prof Edgard Santos Bahia, Brazil 1973

Groups	Patient No	Pressure gradients PA RV D plateau	PA RV D D_2	LV RA D_2 mean
I	2	−2 6	−3 4	−3 1
	4	+0 1	−0 1	−4 8
	5	−6 3	−4 5	−6 7
	6	+0 2	−2 5	−9 0
	7	+0 2	0 0	−5 6
	8	−0 7	+1 7	−7 8
	9	−0 6	−0 2	+2 0
II	1	–	+1 7	+10 0
	3	+3 7	+3 4	+2 2

Abbreviations similar to those in Table II

result mainly from mitral insufficiency, the hemodynamic evidences of obliterative restrictive left ventricular disease being absent.

Three patients in Group I (Nos 2 7, and 9) had a large chronic, pericardial effusion, but their hemodynamic data does not distinguish them from the other patients in the same group (Tables III IV and V)

Finally it is very interesting to consider that, in spite of these profound hemodynamic changes, these patients may survive for a long time after the onset of symptoms of congestive heart failure Patient No 9, for instance, has been under medical care with recurrent ascites and peripheral edema for 17 years Since the myocardium in the chronic established form of the disease, is relatively spared it is possible to suppose that once the patient reaches a certain hemodynamic *equilibrium he can remain* relatively stable for a long time Complications like the recurrence of disease activity which may cause severe myocardial lesions with consequent progressive deterioration of myocardial function,[10] or the onset of a severe arrhythmia, may break this equilibrium and lead to the patient s death

Summary

Nine patients with *endomyocardial fibrosis* have been studied The clinical diagnosis was confirmed by right ventricular angiography in all of them They were submitted to right and left ventricular catheterization and had the cardiac pressures, the pulmonary arteriolar resistance, *and the cardiac index measured The ratio be*tween the end diastolic and systolic ventricular pressures has been taken as an index of the *degree of impairment to ventricular filling* and based on this patients were classified into two groups I, predominant or isolated right ventricular disease (seven patients), and II, predominant left ventricular disease (two patients)

Group I patients were characterized by a right ventricular D_2/S ratio above 60 per cent severe tricuspid regurgitation, a diastolic pulmonary artery pressure slightly lower than the right ventricular plateau and end diastolic pressures and a reversal of the gradient between the left ventricular end diastolic pressure and the right atrial mean pressure, these two latter findings strongly suggesting a diastolic blood flow between the right atrium and the left ventricle

The two patients in Group II did not show evidences suggestive of tricuspid regurgitation or of an early opening of the pulmonic valve Even presenting high values for the left ventricular D_2/S ratio, the pulmonary arteriolar resistance was normal in one patient and mildly elevated in the other patient.

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Table I Clinical and hemodynamic data on patients studied by selective coronary arteriography

Patient No	Age	Diagnosis	Cardiac index (L/min./m.²)	Ejection fraction (%)	No. of injections	Total volume of contrast (ml.)	LVEDP (mm. Hg) Before	LVEDP (mm. Hg) After
1	37	CAD	2 4	55	5	24 5	11 0	13 0
2	47	CAD	3 2	40	8	38 5	26 0	30 0
3	54	CAD	2 5	30	12	78 5	18 0	27 0
4	63	CAD	2.5	53	10	59 5	14 0	22 0
5	58	CAD	2 9	30	12	66 5	23 0	33 0
6	54	CAD	3 3	41	8	55 0	13 8	15 8
7	66	CAD	2 1	38	11	68 0	19 5	25 0
8	43	CM	3 0	15	7	45 0	27 0	28 0
9	36	CM	2 3	60	5	32 5	10 0	14 0
10	44	CM	3 2	40	7	39 0	16 0	20 0
11	33	CM	4 5	55	6	33 5	21 0	23 0
12	48	CM	4 3	37	9	52 0	10 5	10 5
13	48	CM	3 9	53	3	20 0	9 0	10 0
Mean ± S E.M	48 5 ± 2 8		3 0 ± 0.2	42 0 ± 3 5	7 9 ± 0 7	47 1 ± 4 9	16 8 ± 1 7	20 8 ± 2 1

CAD coronary artery disease CM cardiomyopathy LVEDP left ventricular end diastol c pressur obta ned immediately before coronary arteriography a d just afte co cl s n of la t ı tracoronary injection S E.M stand rd error of the mean.

tions of 76 per cent meglumine diatrizoate and sodium diatrizoate (6 0 ± 0 2 ml per injection) were evaluated The total volume of contrast media used for coronary arteriography ranged from 20 to 78 5 ml (mean 47 1 ± 4 9 ml) per patient. Left coronary injections always preceded right coronary injections [7] and left ventriculography was always performed at least 25 to 30 minutes after coronary arteriography to avoid residual effects of contrast media on left ventricular function [5] The mean duration of coronary arteriography was 34 6 ± 2 1 minutes with a range of 22 to 52 minutes

Continuous left ventricular pressures at high and low sensitivities were monitored starting 15 to 20 seconds prior to and ending 60 to 90 seconds after each coronary arterial hand injection Simultaneous coronary arterial systolic and diastolic pressures except during the time of actual injection, and the Lead I electrocardiogram were also monitored All pressures were measured by means of Statham P23Db transducers zero point being at the mid chest level Recordings were made on an Electronics for Medicine DR 12 photographic recorder at paper speeds of 50 mm./per second.

Since rotation of the patient during filming in various projections affected the pressures in reference to the zero point at the stationary transducer [8] left ventricular end diastolic pressures had to be corrected. This correction value was obtained by determination of left ventricular end diastolic pressures while the patient was supine and at 15 30 and 45 degrees of left and right oblique rotation over four to five respiratory cycles prior to coronary arteriography Pressure differences obtained in this manner were appropriately added to or subtracted from the observed values to achieve a projected supine value Left ventricular systolic and coronary arterial diastolic pressures were not corrected since rotation causes minimal effect on these parameters on a per cent basis [8]

Left ventricular end diastolic pressures were measured at a point occurring 0 052 sec after the onset of the Q wave [9] In addition peak values of the first derivative of the left ventricular pressure rise (dp/dt) were calculated from the steepest tangent to the ventricular pressure curves [10] obtained during six injections in two patients who underwent fixed rate atrial pacing during coronary arteriography Reported pressures were obtained by averaging individual values over 20 to 30 beats Left ventricular end diastolic pressure during maximal systemic arterial hypotension was taken as the mean of five beats

Results

Clinical and hemodynamic data with details of the procedure for all patients are shown in Table I Immediately following completion of coronary

Left ventricular pressures during human coronary cinearteriography

John E Madias M D
Edward M Cohen M D
Boston, Mass

Measurement of left ventricular end diastolic pressure before and after left ventricular cineangiography has been established as a useful stress test for myocardial function [1] Recent studies have similarly demonstrated the occurrence of left ventricular pressure elevations following selective coronary cinearteriography Such elevations, when compared to preinjection control values have been reported to occur to a greater degree in patients with myocardial disease In this regard quantification of this effect has also been proposed as a stress test of ventricular function [2,3]

Suggested mechanisms of this elevation of left ventricular end diastolic pressure following coronary contrast injection have included depression of myocardial contractility[3,5] or a volume overload [2] While both of these effects have been demonstrated in experimental and clinical studies, little information is available regarding the time course of these phenomena relevant to the clinical setting [5] The present investigation was therefore undertaken to further characterize the human left ventricular end diastolic pressure response to coronary arteriography By continuously monitoring this parameter and relating it to other hemodynamic variables insight was obtained in the pathogenesis and implications of elevation of left ventricular filling pressure after selective coronary arteriography

From the Thorndike Memorial Laboratory and the Tufts Circulation Laboratory Boston City Hospital and the Departments of Medicine Harvard Medical School and Tufts University School of Medicine Boston Mass

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Reprint requests Dr John E Madias Department of Cardiology Boston City Hospital 818 Harrison Ave Boston Mass *02118*

Materials and methods

After written, informed consent was obtained, observations were made during cardiac catheterization with coronary arteriography and left ventriculography performed for the usual clinical indications The 13 patients studied ranging in age from 33 to 66 years (mean 48 5 years) included seven patients with significant coronary artery disease (greater than 75 per cent stenosis in at least one major vessel save for one patient with a 50 per cent left anterior descending coronary arterial lesion and a syndrome consistent with Prinzmetal s angina) and six patients with idiopathic congestive cardiomyopathy In the fasting state and after premedication with 75 mg of meperidine hydrochloride and 75 mg of sodium pentobarbital administered intramuscularly a small polyethylene catheter (PE 160) was inserted percutaneously by the Seldinger technique into the right brachial artery for the purpose of monitoring systemic arterial pressure Following right heart catheterization and measurement of cardiac output by the method of Fick the polyethylene brachial arterial catheter was replaced with a Cournand woven dacron catheter (5F 100 cm in length internal diameter 0 026 inch outside diameter 0 065 inch United States Catheter and Instrument Company Glens Falls N Y) by means of percutaneous transfer utilizing an 0 025 inch stainless steel wire This latter catheter was passed in a retrograde fashion into the left ventricular cavity and its position was carefully adjusted to avoid ventricular premature beats during deep breath and cough maneuvers Selective left and right coronary cinearteriography was then performed by the percutaneous femoral method of Judkins [6] Responses to 5 4 ± 0 4 (S E M) left coronary and 2 9 ± 0 4 right coronary arterial injec

Table I Clinical and hemodynamic data on patients studied by selective coronary arteriography*

Patient No	Age	Diagnosis	Cardiac index (L/min./m.²)	Ejection fraction (%)	No. of injections	Total volume of contrast (ml.)	LVEDP (mm. Hg)	
							Before	After
1	37	CAD	2.4	55	5	24.5	11.0	13.0
2	47	CAD	3.2	40	8	38.5	26.0	30.0
3	54	CAD	2.5	30	12	78.5	18.0	27.0
4	63	CAD	2.5	53	10	59.5	14.0	22.0
5	58	CAD	2.9	30	12	66.5	23.0	33.0
6	54	CAD	3.3	41	8	55.0	13.8	15.8
7	66	CAD	2.1	38	11	68.0	19.5	25.0
8	43	CM	3.0	15	7	45.0	27.0	28.0
9	36	CM	2.3	60	5	32.5	10.0	14.0
10	44	CM	3.2	40	7	39.0	16.0	20.0
11	33	CM	4.5	55	6	33.5	21.0	23.0
12	48	CM	4.3	37	9	52.0	10.5	10.5
13	48	CM	3.9	53	3	20.0	9.0	10.0
Mean ± S.E.M.	48.5 ± 2.8		3.0 ± 0.2	42.0 ± 3.5	7.9 ± 0.7	47.1 ± 4.9	16.8 ± 1.7	20.8 ± 2.1

*CAD = coronary artery disease; CM = cardiomyopathy; LVEDP = left ventricular end-diastolic pressure obtained immediately before coronary arteriography and just after conclusion of last intracoronary injection; S.E.M. = standard error of the mean.

tions of 76 per cent meglumine diatrizoate and sodium diatrizoate (6.0 ± 0.2 ml. per injection) were evaluated. The total volume of contrast media used for coronary arteriography ranged from 20 to 78.5 ml. (mean 47.1 ± 4.9 ml.) per patient. Left coronary injections always preceded right coronary injections,[7] and left ventriculography was always performed at least 25 to 30 minutes after coronary arteriography to avoid residual effects of contrast media on left ventricular function.[5] The mean duration of coronary arteriography was 34.6 ± 2.1 minutes with a range of 22 to 52 minutes.

Continuous left ventricular pressures at high and low sensitivities were monitored starting 15 to 20 seconds prior to and ending 60 to 90 seconds after each coronary arterial hand injection. Simultaneous coronary arterial systolic and diastolic pressures, except during the time of actual injection, and the Lead I electrocardiogram were also monitored. All pressures were measured by means of Statham P23Db transducers, zero point being at the mid chest level. Recordings were made on an Electronics for Medicine DR 12 photographic recorder at paper speeds of 50 mm./per second.

Since rotation of the patient during filming in various projections affected the pressures in reference to the zero point at the stationary transducer,[8] left ventricular end diastolic pressures had to be corrected. This correction value was obtained by determination of left ventricular end diastolic pressures while the patient was supine and at 15, 30, and 45 degrees of left and right oblique rotation over four to five respiratory cycles prior to coronary arteriography. Pressure differences obtained in this manner were appropriately added to or subtracted from the observed values to achieve a projected supine value. Left ventricular systolic and coronary arterial diastolic pressures were not corrected since rotation causes minimal effect on these parameters on a per cent basis.[8]

Left ventricular end diastolic pressures were measured at a point occurring 0.052 sec. after the onset of the Q wave.[9] In addition, peak values of the first derivative of the left ventricular pressure rise (dp/dt) were calculated from the steepest tangent to the ventricular pressure curves[10] obtained during six injections in two patients who underwent fixed rate atrial pacing during coronary arteriography. Reported pressures were obtained by averaging individual values over 20 to 30 beats. Left ventricular end diastolic pressure during maximal systemic arterial hypotension was taken as the mean of five beats.

Results

Clinical and hemodynamic data with details of the procedure for all patients are shown in Table I. Immediately following completion of coronary

Table II Rate and pressure changes during 103 intracoronary injections*

	Before injection	*At maximal change*	*Time of maximal change (sec.)*	*After injection*
R R interval (sec)	0 80 ± 0 01	0 98 ± 0 02 p < 0 001	6 2 ± 0 4	0 80 ± 0 01 ns
LV systolic pressure (mm Hg)	124 1 ± 1 4	97 9 ± 1 9 p < 0 001	8 4 ± 0 2	122 8 ± 1 5 ns
Coronary diastolic pressure (mm Hg)	71 7 ± 0 9	56 6 ± 1 1 p < 0 001	8 1 ± 0 3	69 7 ± 1 0 ns
LV end diastolic pressure (mm Hg)	20 2 ± 0 7	19 9 ± 0 6 ns	8 4 ± 0 2	20 3 ± 0 6 ns

Rates and pressures reported immediately before injection at the time after commencement of injection when maximal changes occurred, and 60 to 90 seconds after injection at full recover P values refer to the significance of each parameter when compared with the respective value before injection LV left ventricular

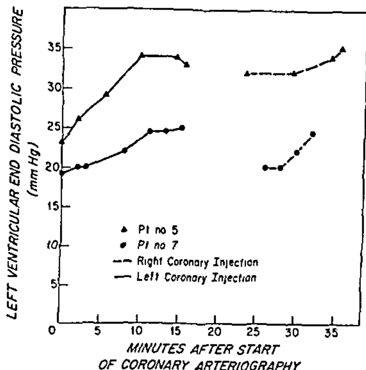


Fig 1 Sequential changes of left ventricular end diastolic pressure in two representative patients after repeated intracoronary injections Each symbol represents a pressure determination obtained just prior to a separate injection pt patient

arteriography 12 of the 13 patients demonstrated increases in left ventricular end diastolic pressures above initial preinjection values (mean elevation 4 3 ± 0 9 S E M millimeters of Hg p < 0 005) One patient with congestive cardiomyopathy hospitalized in the past with pulmonary edema did not respond with such an elevation Although patients with coronary artery disease had a greater elevation than patients with cardiomyopathy, the total volume of injected contrast required for arteriographic delineation was greater in the former group Similarly, the four patients (Nos 3 4 5, and 7) who had the greatest elevations of left ventricular end diastolic pressures following coronary arteriography (mean elevation 8 1 ± 0 9 mm Hg) required more contrast during coronary arteriography when compared to all other patients or to the remaining patients with coronary artery disease Despite this correlation of left ventricular end diastolic pressure elevation with the volume of injected contrast (r = 0 69, p < 0 05) initial left ventricular end diastolic pressure, cardiac index ejection fraction and patterns of left ventricular contraction did not correlate with left ventricular end diastolic pressure rise after coronary arteriography

During repeated coronary injections observed elevations of left ventricular end diastolic pressure occurred in a cumulative incremental fashion The levels so attained were not sustained with respect to time however and returned toward baseline values shortly after a pause in the procedure (Fig 1)

During 103 individual coronary injections maximal systemic hypotension (79 per cent of preinjection values of left ventricular systolic pressures) occurred slightly later than eight seconds after contrast injection Maximal bradycardia (125 per cent of preinjection R R intervals) occurred somewhat earlier (Table II) Alterations in electrocardiographic T waves paralleled systemic hypotension and bradycardia in timing and magnitude Despite these wide variations in systemic arterial pressure and heart rate left ventricular end diastolic pressure remained constant No differences were thus encountered

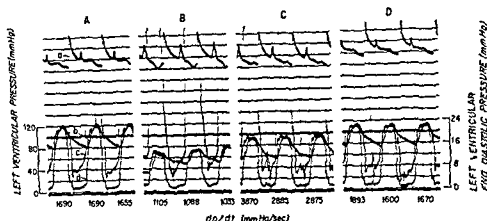


Fig 2 An illustration of the left ventricular and systemic pressure changes recorded during an individual left coronary injection *A*, immediately prior to injection a atrial pacing artifact on the Lead I electrocardiogram b systemic arterial pressure c left ventricular end diastolic pressure recorded at high sensitivity d, left ventricular pressure at low sensitivity *B*, 10 seconds after commencement of coronary injection during systemic hypotension *C*, 18 seconds after injection during partial recovery of systemic arterial pressure *D* 52 seconds after injection dp/dt first derivative of left ventricular systolic pressure rise time lines, 1.0 sec

Table III Hemodynamic changes during atrial paced left coronary artery injections*

	Before injection	*At maximal hypotension*	*During recovery from hypotension*	*After injection*
R R interval (sec)	0.70 ± 0.02	0.70 ± 0.02 *ns*	0.70 ± 0.02 *ns*	0.70 ± 0.02 *ns*
LV systolic pressure (mm Hg)	118.0 ± 2.7	86.0 ± 5.2 p < 0.01	107.1 ± 2.7 p < 0.02	114.0 ± 2.6 ns
Coronary diastolic pressure (mm Hg)	80.5 ± 2.3	60.8 ± 6.6 p < 0.02	70.3 ± 3.0 p < 0.05	75.3 ± 3.4 ns
LV *end diastolic pressure* (mm. Hg)	*12.0 ± 1.6*	*13.2 ± 1.5* ns	*12.0 ± 1.5* ns	*12.1 ± 1.4* ns
LV dp/dt (mm. Hg/sec)	1448 ±129	1074 ±132 p < 0.01	2069 ±251 p < 0.01	1461 ± 131 ns

*Hemodynamic parameters reported immediately before injection, at the time of maximal decrease in systemic arterial pressure, during recovery of systemic arterial pressure 15 to 20 seconds after commencement of injection and at full recovery 60 to 90 seconds after injection P values refer to the significance of each parameter in relation to the respective value before injection LV, left ventricular dp/dt, first derivative of left ventricular systolic pressure rise

among left ventricular end diastolic pressures immediately preceding during or just after individual coronary contrast injections Incremental elevations of left ventricular end diastolic pressures did occur following repeated coronary injections but only when a precoronary injection pressure was compared to the preceding postcoronary value

Similar hemodynamic parameters were continuously monitored during six atrial paced coronary injections (Table III) Pacing at a constant rate did not abolish or attenuate the hypotensive response, mean left ventricular systolic pressure decreasing to 73 per cent of preinjection values. As with unpaced coronary injections left ventricular end diastolic pressure remained constant during the period of maximal hypotension during the recovery period of systemic arterial pressure and up to 90 seconds following coronary injection (Fig 2) The maximal rate of left ventricular systolic pressure rise (dp/dt) abruptly fell to a mean of 74 per cent of its preinjection value after coronary contrast injection This decrease occurred after several beats and paralleled the fall in systemic arterial pressure in time (maximal change 9.4 ± 1.3 sec after injection) During the period of partial recovery of systemic arterial pressure (around 20 seconds after injection) while electrocardiographic T wave alterations still persisted, mean left ventricular dp/dt

was significantly elevated achieving maximal values of 143 per cent of the preinjection value ($p < 0.01$) All of the above hemodynamic parameters returned to preinjection values 60 to 90 seconds after coronary injection (Table III)

Discussion

The increased utilization of coronary arteriography and left ventriculography as diagnostic tools and therapeutic indicators has focused attention on factors related to procedural morbidity and mortality [11] The hemodynamic response to coronary arterial injection of radiologic contrast media may therefore be an important factor influencing patient safety

Prior work by other investigators has demonstrated separate and distinct myocardial and peripheral effects of radiologic contrast media Studies involving left ventricular injection in experimental animals and man have demonstrated responses consistent with an initial Frank Starling length tension effect by virtue of a sudden volume load followed by depression of myocardial contractility and peripheral vasodilation [12 20] Prompt increases in plasma osmolarity associated with subsequent hemodilution and intravascular hypervolemia have been observed and attributed to the hypertonic composition of contrast agents [1 2 20 28]

Experimental observations relevant to intracoronary injection of these agents have similarly demonstrated myocardial depression as well as a diminution in peripheral vascular resistance [4 20 29 30] Other observations have included bradycardia an initial decrease followed by an increase in coronary blood flow and minimal changes in left ventricular end diastolic pressure [20 30 31] The mechanisms mediating these responses are as yet unclear A direct depressant effect of contrast media on the heart is suggested by observations that pacing atropine and bilateral cervical vagotomy do not abolish the negative inotropic effect [32] While bradycardia appears reflexly mediated since it is abolished by parasympathetic blockade,[32 33] peripheral vasodilation has not been influenced by atropine, or alpha or beta adrenergic blockade [32] Some evidence exists however for involvement of an autonomic neural mechanism perhaps mediated by coronary vascular receptors sensitive to volume changes [32]

Studies characterizing the hemodynamic responses during human clinical coronary arteriography have been few in number Benchimol and McNally[34] observed that the hypotension bradycardia, and electrocardiographic repolarization changes observed after coronary arterial contrast injection returned to normal after approximately one minute Since angina pectoris was encountered during the period of maximal T wave change and appeared to parallel its severity they suggested that contrast agents induce myocardial ischemia Gensini and co workers[2] measured left ventricular end diastolic pressures in patients one to three minutes following the last coronary injection. Finding these pressures elevated particularly in patients with coronary artery disease they suggested usage of coronary arteriography as a stress test More recently Kavanaugh Gray[3] also noted elevations in left ventricular end diastolic pressures in patients with diseased or damaged ventricles following both left ventricular angiography and coronary arteriography Such elevations were largely attributed to residual disturbances of myocardial function induced by the contrast media On the other hand others have suggested that such elevations are more likely due to osmotically induced intravascular hypervolemia [2 21]

The present investigation has similarly demonstrated elevations of left ventricular end diastolic pressures following completion of coronary arteriography Elevations occurred however only after a significant time lag and were incremental and cumulative suggesting a primary dependence on an osmotically mediated intravascular volume shift

Several experimental animal studies have demonstrated transient myocardial contractile depression occurring within several heart beats following coronary contrast injection and lasting less than 20 seconds [4 20 3] In addition Zelis and co workers[17] briefly alluded to a prompt diminution in the maximal velocity of contractile element shortening following human left coronary arterial contrast injection Despite these data no clinical information is currently available regarding the time course of recovery of such myocardial depression The present study has demonstrated an abrupt decrease in dp/dt occurring coincident to and paralleling the maximal systemic hypotensive response Since paced heart rates and left ventricular end diastolic

pressures were constant during these injections variations in dp/dt should reflect alterations in myocardial contractility or afterload[35] Although the observed decrease in dp/dt is suggestive of and consistent with the time course of myocardial depression in prior studies the accompanying systemic hypotension renders it invalid as an indicator of decreased contractility The subsequent elevation of dp/dt occurring at a time when systemic arterial pressure is still depressed below control levels should reflect however enhanced myocardial contractile activity since the expected effect of decreased afterload is a diminution in dp/dt[35 36] While a conventional low frequency catheter system was used to determine dp/dt and absolute values may suffer from phase lag[37] directional changes in this parameter should remain valid. From these data any myocardial depression that does exist during coronary contrast injection is a transient event and is promptly replaced during recovery of systemic hypotension by enhanced myocardial contractility Although electrocardiographic repolarization changes tend to parallel the decrease in and recovery of systemic arterial pressure[34] it is also evident that such T wave alterations do not necessarily correlate with myocardial mechanical events

This study indicates stability of left ventricular end diastolic pressures during the course of individual coronary injections of contrast media The hemodynamic correlate of myocardial ischemia early elevation of end diastolic pressure was not observed Our observation of prompt elevation of dp/dt during the recovery phase of systemic hypotension is consistent with the conclusions of prior animal studies and limited clinical observations that the hypotensive response is related to the combined effects of myocardial depression and systemic vasodilation[4 12 17] The late elevations of left ventricular end diastolic pressure observed following such procedures are variable with time and are more likely related to the volume effect of hyperosmotic radiologic contrast media In this regard measurement of this pressure response is a poor indicator of left ventricular function

Summary

Continuous left ventricular pressures were recorded during coronary arteriography performed on patients with coronary artery disease or cardiomyopathy Left ventricular end diastolic pressures remained unchanged during injections but rose in a cumulative, incremental fashion between individual injections Elevation of left ventricular dp/dt accompanied the late phase of systemic hypotension The results suggest prompt recovery of left ventricular function after coronary contrast injection Left ventricular end diastolic pressure elevation was variable with time appeared related to a volume effect, and was a poor indicator of left ventricular function

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Coxsackie Group B virus and primary myocardial disease in infants and children

Prapit Sudhas Na Ayuthya M D
Jidbhong Jayavasu M D D Sc
Boonchob Pongpanich M D
Bangkok, Thailand

In reviewing our clinical materials on heart dis ease in the Pediatric Department at the Ramathibodi Hospital during the four year period (1969 1973) we came across a group of heart diseases which we classified as primary myocardial disease We have used the following criteria for our cases enlargement of the heart and absence of significant heart murmur with nonspecific electrocardiograph (ECG) changes Those cases of myocardial disease such as rheumatic heart disease glycogen storage dis ease cardiac beri beri diphtheritic myocarditis and congenital heart disease were excluded. The remaining patients probably belong to the group with viral myocarditis endocardial fibroelastosis, and myocardial disease of unknown cause

Since at present there is an advance in viral diagnostic procedures an increasing interest in evaluating viruses as etiologic agents in diseases of questionable cause such as many of the myocardiopathies [1] and a scanty number of publications about these diseases in the pediatric age group in Asian countries [2 3] a review of our data is undertaken

Results

During a four year period of study 500 cases of heart disease were seen in the Pediatric Depart ment of Ramathibodi Hospital Of these 392 cases (78 per cent) were diagnosed as congenital heart disease and 108 (22 per cent) cases were diagnosed as acquired heart disease Within the latter group 77 cases were diagnosed as being of rheumatic origin and 18 cases were diagnosed as primary myocardial disease These 18 patients constituted the subjects for analysis

The clinical data for the patients are presented in Table I

The patients ages vary from one month to seven years with a mean age of 1 6 years (only one case was over five years of age) The male to female ratio of patients was 2 1 Patients were seen throughout the year with the peak inci dence in the summer and rainy seasons.

Congestive heart failure was seen in 80 per cent of the cases Of the 15 patients who had hemoglobin determinations performed, the mean hemoglobin was 9 4 Gm per cent Cardiac enlargement was seen in all cases with the mean cardiothoracic ratio of 0 59 (range 0 51 to 0 74)

Table II shows the nonspecific symptoms and signs in the patients Seventy two per cent of the cases had histories suggestive of recent upper respiratory tract infection of viral origin

Cardiac signs and symptoms are presented in Table III The main ECG abnormalities were those of sinus tachycardia and nonspecific ST T wave changes with or without low voltages (Ta ble IV) Ventricular hypertrophy and cardiac ar rhythmia were seen in a minority of the cases

Cardiac catheterization with angiocardiogra phy was performed in four cases in order to ex clude congenital heart disease The data showed mild to moderate degrees of elevated right and left ventricular end diastolic pressures. Chamber dilation of the ventricles was seen on angiograms in all cases One patient (No 18) had evidence of pericardial effusion on right atrial angiogram

Patients outcome Digitalis was administered to all of the patients who were in congestive heart failure Glucocorticoid was used in only one

Fr m th Departments of P d atrics and Pathology Faculty of Medi c ne Ramath bodi Hosp tal, Mahidol Uni ersity Bangkok Thailand.
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Rep t requests to Pr p t Sudhas N Ayuthya M D Departme t of Ped atrics, Faculty of Med cine, Ram thibodi Hospital, Rama VI Road, Ba gkok 4, Th land

Table I Clinical data of patients

Case No.	Age in years: Onset	Age in years: First seen	Sex	Months of onset	C H F	Hemoglobin hematocrit	Chest x ray cardio thoracic ratio	Serologic study for coxsackie B virus	Outcome
1	1/12	1/12	M	April	+	8 5/29	0 55	Nonsignificant rise in titer (negative)	Dead four months later EFE on postmortem
2	2/12	3/12	M	June	+	11 0/33	0 68	Negative	Much improved no symptoms last seen two years later
3	6/12	6/12	F	Jan	+	10 6/30	0 62	Not done	Complete recovery in 1 year
4	7/12	10/12	F	Aug	+	13 3/39	—	Not done	Dead one week later EFE
5	7/12	9/12	M	Jan	−	—	0 57	Not done	Lost to follow up
6	8/12	8/12	F	Jan	+	—	0 74	Not done	Dead two weeks later EFE
7	10/12	10/12	M	March	+	10 2/27	0 69	Negative	Much improved eight months later
8	11/12	11/12	M	Sept	−	9 4/31	0 56	Negative	Improved one month later
9	1 1/12	1 1/12	M	Nov	−	11 9/35	0 6	Not available yet	Improved two months later
10	1 5/12	1 5/12	F	March	+	7 5/23	0 51	Negative	Improved on discharge lost to follow up
11	1 5/12	1 7/12	M	Feb	+	9 3/26	0 69	Coxsackie B3	Dead one year later at home from CHF
12	1 5/12	1 5/12	M	Sept	+	6 0/20	0 64	Coxsackie B3	Improved on discharge lost to follow up
13	1 6/12	1 6/12	M	July	+	5 4/26	0 55	Coxsackie B4	Improved on discharge lost to follow up
14	1 6/12	1 6/12	M	Oct	+	10 4/35	0 58	Coxsackie B4	Dead six months later no autopsy
15	1 6/12	1 6/12	M	Aug	−	7 4/26	0 53	Negative	Improved on discharge lost to follow up
16	1 10/12	1 10/12	F	Nov	+	9 5/33	0 66	Did not return	Improved on discharge
17	5	5	M	Feb	+	−	0 54	Negative	No significant changes in five months
18	7	7	F	June	+	12/36	0 55+ve pericardial effusion	Coxsackie B4	Improved six months later

case Initial clinical improvement was seen in all cases however five patients were dead within one week to one year after having first been seen Three of the cases had postmortem examinations performed in other hospitals and were found to have had endocardial fibroelastosis Seven patients showed signs of improvement after being followed for one month to two years of these cases, one patient had a complete recovery in one year Six patients were lost to follow up so their outcomes were unknown

Virus studies Twelve patients had serologic tests for neutralizing antibody to coxsackie virus performed according to the method described by Milnick and Wenner [4] Among these, five patients (42 per cent showed serologic evidence of recent coxsackie B virus infection (Table V) with coxsackie B 4 and B 3 viruses seeming to predominate

Discussion

Due to the presence of nonspecific symptoms and signs of fever coughing, and respiratory distress in these patients one has to differentiate viral myocarditis from other entities such as pneumonia and bronchitis Many patients were admitted with the symptoms of acute onset of puffy eyelids generalized edema, and respiratory distress thus acute poststreptococcal glomerulonephritis had to be eliminated Sometimes, on clinical examination alone cardiac enlargement cannot always be suspected Many cases in our series were not diagnosed as primary myocardial disease until chest x rays were taken It is our opinion that many patients with primary myocardial disease are missed because the symptoms are not severe

The ECG s of the patients studied were non specific, manifested mainly by sinus tachycardia and nonspecific ST T wave changes Cardiac arrhythmia was found in only 22 per cent of the cases When one suspects primary myocardial disease cardiac catheterization and angiograms are not necessary However, these were done in some of the patients in order to exclude certain types of congenital heart disease, such as an

anomalous left coronary artery arising from the pulmonary artery which could be corrected surgically These studies cannot usually differentiate the type of myocardial disease

The serologic evidence of a recent coxsackie B viral infection in 5 out of 12 (42 per cent) of our patients suggests that coxsackie B infection plays a major role in causing primary myocardial disease This evidence is in agreement with a previous report by Burch and co workers[5] who found coxsackie B virus antigens in approximately 50 per cent of the cardiac specimens obtained from children aged one month to 15 years by means of an immunofluorescent antibody technique

Other viruses can cause myocarditis such as rubella[6] mumps[7] chickenpox[8] influenza[9] and Echo[10] but at a lower frequency than coxsackie B virus Our situation does not permit us to study other viruses

Recently arboviruses were postulated as a cause of primary myocardial disease in adults in Ceylon[11] Our studies of arbovirus infection in the pediatric age group[12] including a long term follow up of these patients do not demonstrate any evidence of myocardial involvement

It is still a matter of controversy as to whether or not primary endocardial fibroelastosis (EFE) can be produced by previous viral myocarditis[13] A recent study of EFE and viral myocarditis by Hutchins and Vie[14] based on clinical and autopsy findings from 64 children supports the hypothesis that some patients with interstitial myocarditis may produce left ventricular dilation of such a duration as to be sufficient for the development of myocardial hypertrophy and EFE Three of our patients who had postmortem examinations were found to have EFE

In a tropical country like Thailand endomyocardial fibrosis (EMF) was found occasionally but usually occurred in the older age group The youngest case reported was eight years of age[15] The clinical data including an ECG and an angiogram, did not support a diagnosis of EMF

Nutritional factors may contribute to primary myocardial disease Anemia which is seen in some of our patients and protein calorie malnutrition were considered to be conditioning factors that contribute to the severity of viral infection[1] Severe protein calorie malnutrition can produce myocardial changes[16,17] and has to be considered as an etiologic factor

Table II Nonspecific symptoms and signs of patients

Symptoms and signs	*No of cases*	*Per cent*
Fever	13	72
Cough or coryza	13	72
Respiratory distress	12	67
Edema	9	50
Diarrhea	3	16
History of frequent upper respiratory infections	3	16

Table III Findings related to the cardiovascular system of patients

Symptoms and signs	*No of cases*	*Per cent*
Cardiomegaly	18	100
Abnormal ECG	18	100
Hepatomegaly	17	94
Congestive heart failure	14	80
Abnormal lung signs	9	50
Gallop rhythm	7	40
Soft heart murmur	2	11

Table IV Electrocardiographic findings in patients

	No of cases	*Per cent*
Sinus tachycardia	18	100
Nonspecific ST T wave changes	13	72
Left ventricular hypertrophy	6	33
Low voltages	4	22
Right ventricular hypertrophy	2	11
Combined ventricular hypertrophy	2	11
Left atrial enlargement	2	11
Right atrial enlargement	2	11
Cardiac arrhythmia	4	22

Atrio entricular dissoci tion = 1
First degre atrioventri ular block = 2
Pr matu e v ntricular contraction = 1

The natural course of primary myocardial disease especially viral myocarditis in the pediatric age group has not been well studied. In newborn infants coxsackie B myocarditis caused a high mortality[18] From our data some patients had a complete recovery while others worsened progressively and died within a short period. Treatment with glucocorticoids can produce improve

Table V Serologic test for coxsackie B virus using heterophil antibody technique

Case No	Type of serum	Serologic titer Coxsackie B1	2	3	4	5	6
11	Acute	<4	<4	64	<4	<4	–
	Convalescent	not done					
12	Acute	<4	<4	<4	32	<4	–
	Convalescent	8	<4	128	32	<4	–
13	Acute	<4	<4	8	128	<4	–
	Convalescent	<4	<4	8	>256	<4	–
14	Acute	<4	<4	<4	<4	<4	–
	Convalescent	<4	<4	8	128	<4	–
18	Acute	<8	<8	<8	<8	<8	<8
	Convalescent	<8	16	<8	64	<8	<8

ment in certain patients [19] but the final outcome was unknown, therefore, a carefully controlled study with a long term follow up is needed

Summary

Eighteen infants and children with the clinical diagnosis of primary myocardial disease are reported Of those cases who had serologic study for coxsackie B performed, 42 per cent were found to indicate a recent infection The data was reported according to its outcome Possible relationships between viral myocarditis and EFE are discussed

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Experimental and laboratory reports

The possible use of ^{125}I labeled fibrinogen for the detection of mural thrombosis following myocardial infarction

Charles P Warlow
Gordon Terry
Aberdeen Scotland

The ^{125}I labeled fibrinogen technique has been used to detect the deposition of fibrin in the deep leg veins following surgery[1,2] myocardial infarction[3,4] and strokes[5] and also in the kidney during renal transplant rejection[6] Several reviews of the technique have recently appeared[7,8] Mural thrombus is found at necropsy in about 44 per cent of patients dying after acute myocardial infarction[10] but it is seldom, if ever diagnosed during life unless systemic embolization occurs. If ^{125}I labeled fibrinogen is administered to patients before the deposition of fibrin in mural thrombus one might expect its detection by a rise rather than the normal fall in the radioactivity recorded over the precordium. Despite the fact that many patients with myocardial infarction have been studied,[3,4] only Simmons Sheppard, and Cox[11] briefly mention four patients in whom the precordial radioactivity did not fall as expected and two of them had mural thrombus at necropsy During the course of a low dosage subcutaneous heparin trial using ^{125}I labeled fibrinogen to detect deep venous thrombosis, we have observed four cases from a total of 83 patients with acute myocardial infarction in whom the precordial radioactivity did not show the expected fall with time

Patients and methods

The four patients were all admitted to a coronary care unit within 12 hours of the onset of symptoms of myocardial infarction They all had unequivocal electrocardiographic evidence of recent transmural infarction On admission potassium iodide was given to block the uptake of iodine by the thyroid gland and, between five and twelve hours later approximately 100μCi of ^{125}I labeled fibrinogen (Radiochemical Centre Amersham England) was administered intravenously Two patients (Cases Nos 1 and 2) received subcutaneous sodium heparin (Weddel Pharmaceuticals Ltd.) 5 000 I U every 12 hours The thyroid the precordium at a point in the fourth intercostal space to the left of the sternum and eight points along the course of the long saphenous vein of each leg were scanned daily for ten days with a Pitman 235 isotope localization monitor No isotope was ad

From the Department of Medicine University of Aberdeen and the Coronary Care Unit, Aberdeen Royal Infirmary Aberdeen Scotland.
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Reprint requests to Dr C P Warlow University Department of Medicine Foresterhill, Aberdeen AB9 2ZD Scotland.

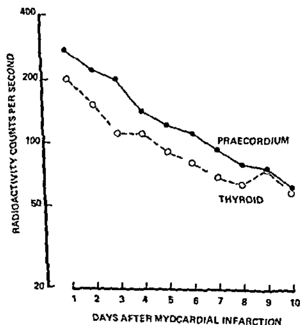


Fig 1

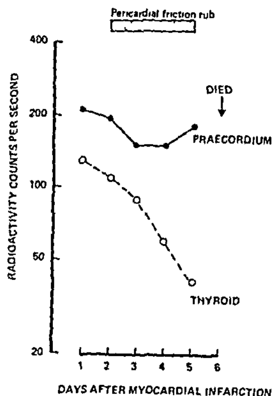


Fig 2

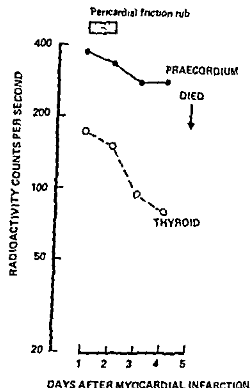


Fig 3

ministered which would spuriously elevate the precordial radioactivity[12]

A typical record of the decay in radioactivity over the thyroid and precordium is shown in Fig 1 This decay is due both to the metabolism of fibrinogen and the physical decay of the ^{125}I Normally, the activity declines exponentially over both sites at approximately the same rate

Results

Clinical details of the four patients are shown in Table I and the rate of decline of precordial and thyroid radioactivity is shown in Figs 2 through 5 Case 1 had evidence of pump failure from the time of admission and developed a pericardial friction rub two days after infarction On the sixth day he developed acute circulatory failure despite being in sinus rhythm and died. Necropsy revealed extensive fibrinous pericarditis together with an extensive mural thrombus Death was due to cardiac tamponade secondary to left ventricular rupture Case 2 had a similar clinical course and died on Day five Necropsy findings were similar but the pericarditis was less marked Case 3 developed ventricular fibrillation on admission and after resuscitation showed evidence of left ventricular failure On Days three to five a pericardial friction rub was heard and on Day eleven he developed a left hemiparesis attributed to embolization from mural thrombus This resolved and he was discharged home Case 4 developed mild left ventricular failure and also had a pericardial friction rub on Days one and two His progress was uneventful, apart from a deep venous thrombus and he was discharged home

Discussion

From among 83 patients with acute myocardial infarction being studied with ^{125}I labeled fibrinogen for evidence of deep venous thrombosis, we have found four patients in whom the precordial level of radioactivity did not decay at the normal rate Two patients had necropsy evidence of mural thrombus and a third patient had a cerebrovascular accident presumably due to embolization from mural thrombus. All four patients had clinical evidence of pericarditis and Case 1 had extensive fibrinous pericarditis at necropsy which might explain the rise in precordial radioactivity However 14 other patients developed clinical pericarditis with a friction rub without any evidence of a rise in precordial radioactivity It has been reported that coronary artery thrombosis may occur after myocardial infarction[13] but it is unlikely that enough ^{125}I labeled fibrinogen would be incorporated into a coronary artery thrombus to account for the changes in radioactivity we have observed We suggest therefore that a sustained or rising pre

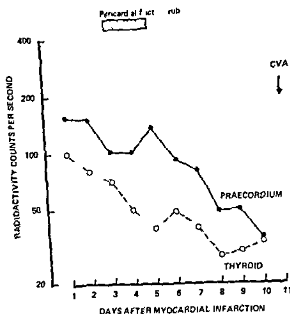


Fig 4

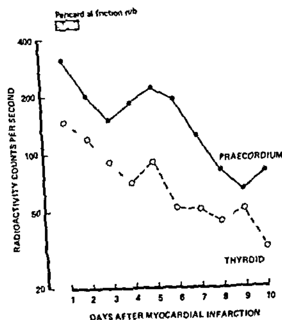


Fig 5

Table I Clinical details of four patients with abnormal decay of precordial radioactivity after the administration of 125I labeled fibrinogen

Case no	*Age*	*Sex*	*Site of infarction*	*Peak SGOT (I.U./L.)*	*Complications*	*Outcome*	*Heparin*
1	6?	M	Anterior	174	RBBB + LAH LVF pericarditis	Died, cardiac rupture (Day 6)	+
2	62	M	Anterior	243	Pericarditis LAH	Died cardiac rupture (Day 5)	+
3	53	M	Anterior	> 100	VF on admission LVF pericarditis, left hemiparesis (Day 11)	Discharged home	−
4	49	M	Anterior	> 100	Pericarditis LVF venous thrombosis	Discharged home	−

RBBB Right bundle branch block LAH Left anterior hemiblock LVF Left ventricular failure VF Ventricular fibrillation

cordial radioactivity level may indicate the development of mural thrombosis Transient rises in activity are not uncommon and might easily be due to error in reading a ratemeter or a change in background radioactivity in the ward. However Cases 1 3 and 4 all showed a sustained or increased radioactivity for two or more days. Case 2 showed no decrease for one day and died the following day before scanning could be performed he did however show a marked discrepancy between thyroid and precordial radioactivity None of the other patients showed an increased or sustained rise in precordial radioactivity for more than 24 hours Six of these patients died during the course of the study and necropsy was performed on three of them In these three patients there was no evidence of either pericarditis or mural thrombus The low mortality rate is due to the fact that patients who were moribund or in cardiogenic "shock" were excluded from entry into the trial None of the 79 patients with a normal fall in precordial radioactivity developed any sign of systemic embolization during the period of study It would appear therefore that using 125I labeled fibrinogen it may be possible to detect the development of

mural thrombus before the occurrence of peripheral embolization This conclusion must of necessity, be cautious and of a preliminary nature since the numbers of patients involved were small Without further study of necropsy material it cannot be definitely stated that the rising precordial radioactivity is not due to the deposition of fibrin outside mural thrombus in for example, the pericardial cavity or coronary artery thrombus Nevertheless when ^{125}I labeled fibrinogen is being used in patients with acute myocardial infarction, a sustained rise in the precordial radioactivity should alert the investigator to the possible if not the certain development of mural thrombosis Whether this knowledge would allow of treatment to prevent embolization is uncertain This conclusion is not dissimilar to the one made over a hundred years ago by Bristowe[14] who wrote, 'And in truth, if it were possible to diagnose their presence I suspect that the knowledge thus obtained would be far more for the gratification of the physician than for the benefit of the patient'

Summary

Four patients with myocardial infarction are described in whom there was either a sustained rise, or a delayed decay of precordial radioactivity after the administration of ^{125}I labeled fibrinogen Two patients had necropsy evidence of mural thrombus and one patient developed a cerebrovascular accident This technique might, therefore detect the development of intracardiac mural thrombus before embolization occurs

We would like to thank the physicians of the Aberdeen Royal Infirmary for allowing us to study their patients and Mrs Rosemary McIntosh for undertaking the scanning

Necropsy studies were undertaken by Drs. E Gray and R A. Keenan

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Tritiated digoxin XX Tissue distribution in experimental myocardial infarction

A J Thompson Major USAF MC*
J Hargis MD
M L Murphy MD
J E Doherty MD
B ooks Air Force Base Texas and Little Rock, Ark.

Experimental myocardial infarction has been reported to increase myocardial sensitivity to digitalis glycosides [1-5] The controversy surrounding the possible hazards of digitalis administration in acute myocardial infarction has been the subject of a number of reports and reviews [6-11] Pathologic studies demonstrate islands of viable myocardium in areas of infarction [12] and electrophysiologic studies reveal electrically unstable areas in infarcted and ischemic myocardium [13, 14] Recent evidence suggests that intoxication with digitalis glycosides may occur at lower serum concentrations in patients with atherosclerotic heart disease and myocardial infarction [15, 16] The known digitalis effect of enhanced automaticity in Purkinje fibers and focal re excitation of ventricular muscle[13] led us to investigate the concentration of tritiated digoxin in normal ischemic and infarcted left ventricular myocardium in an effort to more clearly define the role of digitalis in myocardial infarction

From the D partm nt of Medicine Division of Cardiology Uni ers ty of A kansas Medical Cente a d th Veterans Administrati n Ho pi tal, Little Rock, Ark

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Reprint requests to A. J Thompson, M jor USAF MC USAF/SAM/NGI Brooks Air F rce Base Texas 78235 o Dr J E Doherty D rector D vision of Cardiology VA UAMC Complex, 300 E. Roose elt Rd. Little Rock Ark 72206.

Dr Thompson is urrently with th Cl cal Scien es Di is on, United States Ai Force School of Aerospa e Medicine A rospac Medical Divi ion, United States Air F rce Brook A F rce Base Texas.

Materials and methods

Eleven healthy mongrel dogs* weighing an average of 18 1 kilograms (± 1 4 kilograms S E M) were anesthetized with pentobarbital (25 mg per kilogram of body weight) Ventilation with room air was maintained with an endotracheal tube and respirator The femoral artery was cannulated for continuous pressure monitoring and sampling of blood. The external jugular vein was cannulated for administration of drugs Electrocardiographic Leads I aV_L and the arterial pressure were displayed and recorded (50 mm per second) on a multi channel Electronics for Medicine recorder

Following left thoracotomy ligation of the anterior interventricular coronary artery between the first and second perforating branches produced an anterolateral myocardial infarction All animals developed ST segment elevation and Q waves characteristic of infarction Ventricular arrhythmias developed in a number of experiments and were treated when necessary with intravenous lidocaine

Five minutes after ligation of the coronary artery 0 5 mg of tritiated digoxin was given intravenously The tritiated digoxin which was prepared by the Wilzbach hydrogen exchange method [17] was chemically and chromatographically pure [18] The specific activity of the lots used were 125 mCi per milligram and 161 mCi per milligram. Arterial blood for serum digoxin deter

*The nimals in olved in th s study we e maintained and used n acco dance with the Animal W lfare Act of 1970 and the Gu de for the Ca e and Use f Laboratory Animals prepared by the National Academy of Sc enc s National Research Council

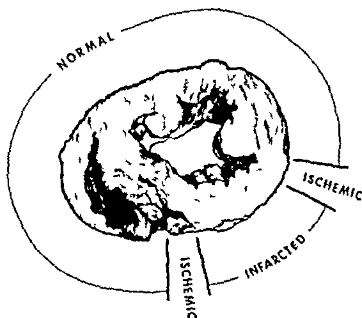


Fig 1 Cross sectional tissue slice through the ventricles As differentiated by the vital dye the normal myocardium stains dark green the ischemic border zone is gray and the area of normal coloration represents the infarcted zone Tissue samples were taken from each zone to determine tritiated digoxin content and oxidative phosphorylation measurements

mination was collected at 5, 10, 15 30 45 60 90 and 120 minutes from the time of digoxin administration Two hours following the administration of intravenous tritiated digoxin a vital dye (20 mg per kilogram of 10 per cent solution of alphazurine 2G) was rapidly injected into the venous catheter

The heart was quickly removed from the chest and immediately taken into a tissue preparation room where all further dissections were done Following cross sectional slicing of the heart full thickness tissue samples were taken from the normal, ischemic and infarcted zone Tissues were weighed and homogenized with a small amount of distilled water The individual specimens were extracted with chloroform and passed through an alumina column The column was eluted with 2 1 chloroform ethanol mixture The eluate was evaporated, the counting solution was added, and radioactivity was measured with a liquid scintillation spectrometer (Packard Tri Carb 21) The results were expressed as nanograms of tritiated digoxin per milliliter for serum and nanograms of tritiated digoxin per gram of wet weight, for tissue The differentiation between the zones was determined by dye distribution (Fig 1)

The polarographic oxygen electrode technique was used to study mitochondrial respiration and oxidative phosphorylation[19 20] of normal and infarcted myocardium in six experiments The mitochondrial pellet was prepared from approximately 7 Gm of myocardium which was washed with homogenizing solution, minced and homogenized[21] Differential centrifugation was then carried out and the mitochondrial pellet was suspended in malate or glutamate substrate All tissue was processed at 0 to 4° C and studies began in less than 90 minutes after death of the animal Simultaneous determination of the normal and infarcted myocardium in the two substrates allowed maximal comparison Mitochondrial oxygen consumption (microatoms of oxygen consumed per milligram of mitochondrial protein per minute) ADP/O ratio (micromoles of adenosinediphosphate [ADP] phosphorylated per atom of oxygen consumed) and respiratory control index (the ratio of oxygen consumption in the presence of ADP compared to that after ADP) were determined for each tissue and substrate[21] Mitochondrial protein was determined by standard methods and ADP assays were determined spectrophotometrically

Results

Serum samples taken at frequent intervals after the intravenous administration of 0 5 mg of tritiated digoxin revealed rapid disappearance of digoxin from the serum Within a 2 hour period after 0 5 mg of digoxin was administered intravenously the serum concentration fell from approximately 35 ng per milliliter at five minutes to 2 1 ng per milliliter (Fig 2) It has previously been documented that this rapid fall in serum concentration primarily represents organ distribution and binding[22] and that two hours allow for equilibration of the serum and tissue compartmentally

Myocardial tissue samples taken two hours after the intravenous administration of 0 5 mg of tritiated digoxin revealed a significant variation in digoxin concentration in and around the infarcted zone (Fig 3) The concentration of 90 ng of tritiated digoxin per gram of normal left ventricle and a tissue to serum ratio of 43 1 is in close agreement with findings previously published by this laboratory[23] The infarcted tissue demonstrated a tissue to serum ratio of 12 1 a 3 to 4 fold decrease in tritiated digoxin content as compared to normal myocardium The

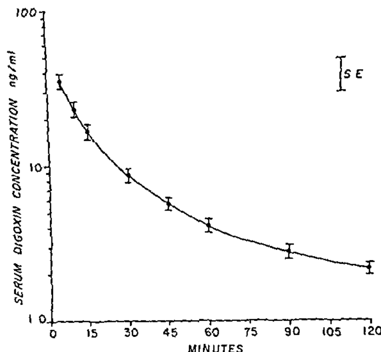


Fig. 2 Serum disappearance curve of ^3H digoxin following the intravenous injection of 0 5 mg of ^3H digoxin. The serum concentration (mean ± S E M) is plotted on the vertical axis with semilogarithmic scale and time on the horizontal axis

Table I

Experiment No	Weight (Kg)	^3H digoxin dose (mg)	Serum concentration (ng/mL)	Wet weight (ng/Gm.) Normal LV	Ischemic LV	Infarcted LV	RV	Atrium	Pericardial fat
1	13 6	0 5	2 32	150 35	130 35	9 51	92 48	73 98	3 95
2	18 0	0 5	1 54	84 51	38 35	18 92	55 32	38 69	—
3	14 1	0 5	1 85	74 28	13 71	7 71	55 10	44.41	2 38
4	23 2	0 5	2 22	105 50	39 18	33 30	67 70	1 06	—
5	14.5	0 5	3 26	114 22	106 26	48 43	88 16	70 33	4 66
6	22 7	0 5	1 48	66 10	41 08	28 54	46 91	28 76	1 68
7	12 7	0 5	3 38	163 17	99 95	27 92	127 09	73 23	4 95
8	16 4	0 5	2 43	70 88	70 34	26 54	58 26	32 15	2 01
9	17.3	0 5	2 17	69 75	66 61	49 82	64 07	38 17	2 46
10	25 5	0 5	0 90	52 26	33 60	11 60	45 71	23 85	0 43
11	20 9	0 5	1 76	29 37	23 57	1 53	37 42	12 65	1 50
Mean	18 1	0 5	2 12	89 13	60 27	23 98	67 07	45 45	2 51
S.E M ±	1 4	—	0 67	28 19	19 06	7 58	21 21	14.37	±0 51

ischemic zone was intermediate between normal and infarct, and a myocardial tissue level of 55 ng per gram and ratio of 26 1 was present

The serum concentration of tritiated digoxin in the cardiac tissues sampled in each of the eleven animal preparations is listed in Table I

Tissue samples from the right ventricle atrium and pericardial fat were analyzed for digoxin content. The normal right ventricle contained less digoxin per gram of tissue than did the normal left ventricle Atrial tissue concentrated less digoxin per gram of tissue than did either ventricle The pericardial fat had a digoxin concentration not significantly different from that of serum.

Listed in Table II are the data evaluating the

Table II

Experiment No	QO_2		RCR		ADP O	
	Normal	Infarct	Normal	Infarct	Normal	Infarct
3	0 4791	0 0856	3 61	2 12	2 31	1 87
5	0 3979	0 1649	3 87	2 97	2 38	2.56
6	0 3003	0 0957	4 02	2 35	2 78	2 15
7	0 2895	0 0977	3 78	3 03	2 75	2 09
10	0 2890	0 0823	4 31	2 21	2 89	2 17
11	0 2867	0 0867	4 24	2 29	2 63	2 30
Mean	0 3404	0 1023	3 97	2 50	2 62	2 19
SEM ±	0 036	0 014	0 12	0 18	0 10	0 10

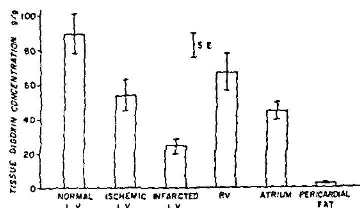


Fig 3 Myocardial concentration of ^3H digoxin. Tissue samples were taken two hours after the intravenous administration of 0 5 mg of ^3H digoxin Digoxin concentration in nanograms per gram of wet weight tissue (mean ± S E M) is on the ordinate Concentration in the normal left ventricle is approximately 90 ng per gram of tissue The ischemic left ventricle and the infarcted left ventricle contained 54 and 25 ng per gram of tissue respectively The normal right ventricle tritiated digoxin concentration of 64 ng per gram of tissue is less than the normal left ventricular myocardium Atrial tissue contains less tritiated digoxin than either ventricle Pericardial fat has a concentration of tritiated digoxin equivalent to serum

metabolic activity of mitochondria from normal and infarcted myocardium in six of the animal preparations Tissue respiration in malate substrate—as measured by oxygen consumption respiratory control index, and ADP/O—is significantly reduced in the infarcted tissue verifying tissue hypoxia and altered mitochondrial integrity in the infarcted zones.

Discussion

The normal ischemic, and infarcted myocardial zones were easily differentiated with a vital dye This rapid and accurate method required no specialized equipment. Oxidative phosphorylation determination confirmed the division of tissue into normal and infarcted regions by demonstrating impaired oxygen utilization of mitochondria from infarcted myocardium Right ventricular myocardium has been shown to concentrate less digoxin than the left ventricle per gram of tissue weight. Atrial tissue concentrates less digoxin than either ventricle, and pericardial fat appeared to have no tissue to serum gradient.

The studies revealed a marked disparity of tritiated digoxin distribution in the canine left ventricle after acute myocardial infarction Homogeneous distribution of tritiated digoxin in the normal canine left ventricle has been demonstrated in previous studies [23, 24] After intravenous administration myocardial concentration of tritiated digoxin peaks at one hour and is well maintained for 12 hours in the canine[25] therefore the two hour tissue samples should be representative of maximal myocardial concentration Altered regional blood flow to ischemic myocardium may explain the distribution pattern of tritiated digoxin as suggested by radioisotope studies utilizing labeled carbonized microspheres[26, 27] and ^{131}I iodoantipyrine [28] The ischemic myocardium may also show reduced tritiated digoxin uptake due to high extracellular potassium concentration[29] which accumulates from cellular injury and intracellular potassium loss

Normal myocardium has a tissue concentration and tissue to serum ratio which closely agrees with previous findings in our laboratory The myocardial digoxin content decreases progressively in normal ischemic and infarcted

tissue with a marked tritiated digoxin gradient being present between these respective zones Disparate repolarization and the initiation of re entrant ectopic rhythms have been demonstrated in ischemic myocardium[13,14] Canine Purkinje fibers exhibit enhanced automaticity in the presence of hypoxia and fiber stretch[30] The similar digitalis effect of enhanced automaticity of Purkinje fibers and facilitation of ectopic rhythms is potentially additive in the ischemic myocardium[31,32] Thus a marked digoxin gradient between normal ischemic and infarcted myocardium may potentiate the appearance of ectopic rhythms from electrically unstable ischemic or infarcted myocardium

Summary

The role and potential hazards of digitalis glycoside administration in acute myocardial infarction remain controversial We investigated the concentration of tritiated digoxin in normal ischemic and infarcted left ventricular myocardium of the dog after ligation of the anterior interventricular coronary artery The normal homogeneous distribution of tritiated digoxin in the normal canine left ventricle was altered following acute myocardial infarction The ischemic and infarcted zones exhibited a marked diminution in digoxin concentration Oxidative phosphorylation determinations confirmed tissue hypoxia in the infarcted zone The gradient of digoxin concentration between normal ischemic, and infarcted zones of myocardium may potentiate the development of an arrhythmia in the electrically unstable infarcted myocardium

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The response of the canine heart to double pulses of short duration A simple addition principle

H Schneider Ph D
G Koning M.Sc E E Ph D
H G Goovaerts E E
Amsterdam, The Netherlands

Why the heart in vivo contracts after the administration of an electrical stimulus is a question which cannot be answered at this moment. Considerable research is being carried out to study by phenomenologic experiments the effects which occur as a result of current passing through the heart muscle The application of electrical stimuli to study heart excitation has been practiced for many years.

A great deal of work has been done in the field of heart electrophysiology and therefore we shall not review the literature published in this field in detail

Generally it can be expected that the effects produced by passage of current through the membrane of a heart muscle cell either in the resting state during activity or after stimulation provide interesting information regarding the nature of the membrane properties It is also possible with the help of intracellular microelectrodes to study changes of the transmembrane potentials resulting from stimulation

The purpose of our experimental work on dog hearts in vivo is not to study the *details of electrophysiologic* changes of the heart muscle under the influence of electrical stimuli but rather to study the behavior of the heart considered as a system first, without examining in detail the macro or microstructure The reason that we wish to stimulate the heart by means of electrical stimuli is because these stimuli can be offered quantitatively in a short interval of time and locally

Experimental set up

For double pulse stimulation use has been made of a digitally programmed stimulator This unit delivers two pulses of a duration that is adjustable from 10 μs to 9 990 ms

The timing between these pulses is also adjustable between 10 μs and 9 990 ms The double pulse configuration can be applied either in a recurrent mode or triggered on the R wave of an electrocardiogram (ECG)

In the latter case the possibility exists of applying a double pulse after a certain number of R waves which number can be preset on the stimulator Application of the double pulse configuration is always preceded by a delay started by the trigger that is adjustable from 0 1 ms up to 999 9 ms.

The pulses are available on two different transformer coupled current sources supplied by an r f carrier in order to prevent distortion of the pulses[1,2] Administration of the double pulse is possible after a certain preset number of R R intervals

The amplitude of the current sources is adjustable from 0 1 mA to 9 9 mA in steps of 0 1 mA and from 1 mA to 100 mA in steps from 1 mA Stabilization will be guaranteed over a load impedance up to 1 kΩ so the pulses are not distorted by the electrode tissue interface All parameters are set by means of thumbwheel switches The block diagram is shown in Fig 1 Whether a combination of the two pulses is followed by one electrical ventricular extrasystole of the heart can be checked with the help of the

From the Department of Medical Physics van der Boechorststraat 7 Free University Amsterdam, The Netherlands.

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Reprint requests to: Dr H Schneider Department of Medical Physics van der Boechorststraat 7 Free University Amsterdam, The Netherlands

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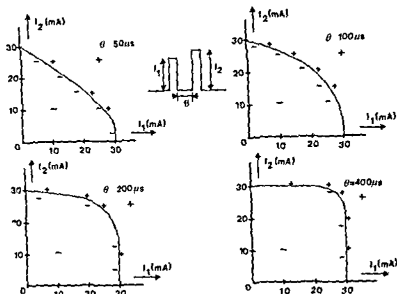


Fig 3 Graphic representations of the measuring results in the (I_1 I_2) plane with θ as the parameter Insertion depth of the electrodes is 1 5 mm Diameter 0 5 mm

Results of experiments with unipolar cathodal or anodal stimulation in the case of rectified and opposite pulses as shown in the graphic representation (Fig 4) indicate clearly the difference in cathodal and anodal stimulation threshold. With an insertion depth of 1 mm of the electrode we measured for the cathodal threshold 20 mA and for the anodal threshold 60 mA

For the sake of clarity the areas are marked with a (+) in which the heart gives an adequate reaction The individual measuring points are omitted. The graphic representation (Fig 4) is given for the time intervals $\theta = 20$ 50 100 200 and 500 µs

The results of the measurements shown in Figs 3 and 4 lead to the following conclusions (1) For values of $\theta < 50$ µs the addition principle for the heart is nearly valid within the experimental error That is to say that the sum of the amplitudes $I_1 + I_2$ of the double pulse determines whether or not there is one electrical ventricular extrasystole (2) For values of $\theta > 400$ µs the graphic relation between I_1 and I_2 is a square That means that for the time intervals $\theta > 400$ µs the pulses I_1 and I_2 are acting independently on the heart. This always results in one ventricular extrasystole In the majority of the experiments, we did not find an exact square but rather a rounded curve (Fig 3) This effect is due to the experimental error (3) If we review the experimental results for the determination of the stimulation threshold as a function of I_1 and I_2 with θ as the parameter represented in Figs 3 and 4, we are struck by the asymmetry around a 45 line drawn from the origin This asymmetry was found to be reproducible in measurements on the right ventricle of ten dog hearts in vivo (4) The addition principle for opposite pulses is still valid in quadrants II and IV (Fig 4) There is a difference in anodal and cathodal stimulation threshold (5) The memory time of the heart is roughly calculated in the order of 500 µs

Discussion

In the first part of this article we described the experimental results with double pulses of short duration which were administered to the dog heart in vivo

We established the graphic relation in determining the stimulation threshold which exists between I_1 and I_2 with the respective time intervals θ as a parameter We shall try to explain the experimental results Tissue will respond to electrical stimuli It is a fact that an active response of the tissue will occur if the current passing through the cell membrane reaches a certain value—the stimulation threshold. Generally speaking the existing theories of excitation are based on experimental observations and measurements

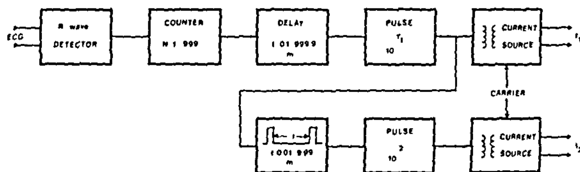


Fig 1 The block diagram of the stimulator unit

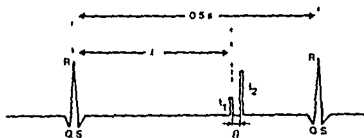


Fig 2 The double pulse in a phase point of the heart cycle

ECG which is registered with a direct recorder and a cathode ray tube

In this way we also have control of the configuration of the ECG of the dog during the experiments The temperature at which the measurements were made amounted to 37° C The temperature control was carried out with a calibrated thermistor in a bridge circuit Chemical parameters were controlled The timing diagram in Fig 2 shows the application of the double pulse in the heart cycle

As a first step in our experiments with double pulses of short duration and rectangular configuration we applied a double pulse with rectified block pulses with a duration τ of 10 μs each on the right ventricle of the exposed dog heart in vivo The experiments were done on 10 anesthetized dogs The amplitudes of the two pulses can be varied from 0 to 100 mA, independently of each other this is also the case for the respective time distance θ from 10 to 10^5 μs

Use was again made of bipolar stimulation with the help of platinum electrodes of which the respective distance (1 0 cm) is large in respect to the individual insertion depths (1 5 mm) and diameters (0 5 mm)

The measurements were made at phase point 250 ms (ν) after the derived trigger pulse from the R wave of the QRS complex of the ECG The double pulse did not occur on the T wave[1]

Results of the measurements

During the measurements, attention was given to a constant repeat frequency of the dog heart (R R intervals ~ 500 ms) The experimental results are graphically represented in the (I_1 I_2) plane with θ as the parameter For values of θ = 50 100 200, and 400 μs the (I_1, I_2) graphic relation is made up to determine the stimulation threshold of the heart These series of measurements are repeated with ten dogs for the θ values mentioned For an electrical ventricle extrasystole a plus (+) is entered and for no effect a minus (−) It should be noted that these measurements with the double pulses were made in any sequence In Fig 3 the experimental results are entered as examples in the (I_1 I_2) plane for a θ = 50 100 200 and 400 μs As can be seen in Fig 3 between the (+) and (−) points a curve is drawn which stands perpendicular to the I_1 axis The experimental error of the curve drawn is ± 5 per cent Generally it can be said that to the left of and below the curve the heart showed no electrical ventricular extrasystole while to the right of and above the curve the heart reacted with a ventricular extrasystole (adequate) to the double pulse of short duration The curve intersects the I_1 and I_2 axes at 30 mA The surface of the electrodes which is in contact with the tissue, determines the current density in the surrounding tissue

This threshold value is a function of the electrode surface For the sake of completeness it has to be noted that the significance of the points of intersection on the I_1 and I axes is that the heart reacts then to one single pulse It also appeared that for fixed subliminal values of I_1 and I_2 the value for θ is accurate up to 5 μs for obtaining an electrical ventricular extrasystole with a respective electrode distance of 1 cm

influence was a raising of the stimulation threshold for both anodal and cathodal stimulation. Chemical parameters were controlled. We observed that the pulses I_1 and I_2 were independently working on the heart at a time interval θ of 1 000 μs that is to say that the decay time E_1 is much slower.

A larger value for the decay time results in a very small rise time of the excitatory state with the result an excitatory state with a greater amplitude by the same current amplitude as without extra KCl. The threshold is reached very easily. That means because the building up of the excitatory state goes easier a smaller current strength gives cause for reaching the excitation threshold. In other words the current strength threshold is reduced.

However we measured a larger value for the threshold. As the result of this effect the threshold in the heart must be increased by the extra KCl concentration.

So the extra KCl concentration has two effects (1) a longer decay time with a larger value of the excitatory state and (2) a larger value for the excitation threshold.[4,7] The memory time of the heart is longer (~ 1000 μs) In a normal case after calculation the decay time is ~400 μs. It can be argued if the double pulse method is a good tool to detect ion disturbances and areas with ischemia in the heart muscle.

Summary

Experiments are done with rectified and opposite double pulses I_1 and I_2 with a duration of 10 microseconds each applied to the right ventricle of the dog heart.

The double pulse with a time interval θ between the pulses is applied after a certain time delay ν after the R wave in the heart cycle of the dog. Care is taken that the double pulse was not administered during the T wave.

If a certain combination of amplitudes I_1 and I_2 with a fixed θ was followed by one electrical ventricular extrasystole a (+) was entered in the graphic representation. If not, a (–) was entered.

Graphic representations of the stimulation threshold in the (I_1 I_2) plane were made up with the respective time interval θ between the pulses as parameters.

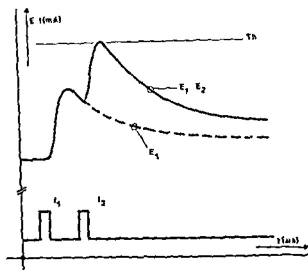


Fig 5 The resulting effect function ($E_1 + E_2$) from ($I_1 + I_2$)

From the experiments it is concluded. (1) for $\theta < 50$ μs the addition principle for the heart is nearly valid, (2) for $\theta > 500$ μs the pulses I_1 and I_2 are working independently on the heart and (3) for $\theta > 1000$ μs the pulses I_1 and I_2 are working independently with a 2 per cent KCl solution disturbance.

The memory time is, possibly a parameter to detect abnormalities in ion concentrations in the heart muscle.

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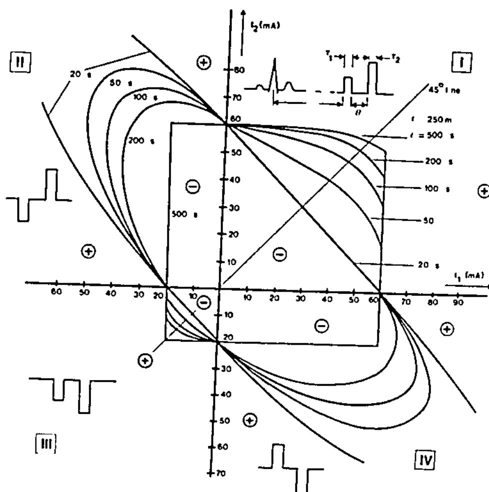


Fig 4 Graphic representations in the four quadrants (I_1 I_2) with θ as the parameter Insertion depth of the electrode is 1 mm Diameter 0 5 mm

Blair[3] quantified the build up of the excitatory state, assuming that there is a quantity called 'the excitation, that increases at a rate which is proportional to the amplitude of the current pulse applied to a cell

Hill[4] has pointed out one very significant factor in excitation the threshold may rise at the same time the local ' excitatory state is building up as the result of passage of an electrical current. When a second stimulus comes the threshold is actually the difference between the excitatory state and the existing absolute threshold ' In our case the threshold will remain constant because the pulses I_1 and I_2 are very short in duration ($\tau = 10\ \mu s$) The result of the Hill[4] condition is that the state of excitation rises exponentially, if the rectangular pulse is then ended the excitatory state will decay toward the original resting state This decay is also exponential with a certain time constant

In our case we construct a theory based on Hill s theory We assume that the current pulse to the heart results in "an effect (excitatory state) which is proportional to the current pulse amplitude and which can be found on administering different current pulses by linear addition When we consider the case of the two pulses I_1 and I_2 the total effect E is given by

$$E_1 + E_2$$

in which E_1 is the effect from I_1, and E_2 the effect from I_2

We obtain a ventricular extrasystole when the following equation is valid (Fig 5)

$$E_1 + E_2 > Th$$

in which Th represents the threshold.

When we assume that E_1 and E_2 are based on the differential equation for diffusion we can construct a mathematical model Then we obtain the same asymmetric graphic representations found in the experiments[5,6]

The addition of electrical energy does not take place in the form of polarization of the electrode It is proved when we disturb the normal equilibrium by the addition of a 2 per cent KCl solution to the heart This solution was supplied through a vein in one of the dog s legs The direct

influence was a raising of the stimulation threshold for both anodal and cathodal stimulation Chemical parameters were controlled We observed that the pulses I_1 and I_2 were independently working on the heart at a time interval θ of 1 000 μs that is to say that the decay time E_1 is much slower

A larger value for the decay time results in a very small rise time of the excitatory state with the result an excitatory state with a greater amplitude by the same current amplitude as without extra KCl The threshold is reached very easily That means because the building up of the excitatory state goes easier a smaller current strength gives cause for reaching the excitation threshold In other words the current strength threshold is reduced

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So the extra KCl concentration has two effects (1) a longer decay time with a larger value of the excitatory state and (2) a larger value for the excitation threshold[4,7] The memory time of the heart is longer (~ 1000 μs) In a normal case after calculation the decay time is ~400 μs It can be argued if the double pulse method is a good tool to detect ion disturbances and areas with ischemia in the heart muscle

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Graphic representations of the stimulation threshold in the (I_1 I_2) plane were made up with the respective time interval θ between the pulses as parameters

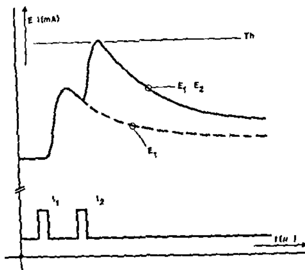


Fig 5 The resulting effect function ($E_1 + E_2$) from ($I_1 + I_2$)

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The memory time is possibly a parameter to detect abnormalities in ion concentrations in the heart muscle

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The effect of pentaerythritol tetranitrate pretreatment on experimental coronary occlusion

Walter D Meester M D , Ph D
Gordon L Van Harn M S Ph D
Grand Rapids Mich.

Nitrites and nitrates are commonly used for treatment of angina and ischemic heart disease The efficacy of nitroglycerin in reducing attacks of angina has been reported frequently [1 2] One of the nitrates pentaerythritol tetranitrate (PETN) is used because its action is similar to that of nitroglycerin[3] however PETN is less effective than nitroglycerin but does act longer [4]

Clinical tests of the effectiveness of PETN produced conflicting results There are reports of a lower mortality rate and 'improved well being in patient with acute myocardial infarction[5] treated with PETN Reduced angina attacks and increased tolerance to exercise before onset of angina with PETN has also been reported [4 6] However there are also reports of the ineffectiveness of PETN treatment Double blind studies comparing the effectiveness of PETN and a placebo have shown no significant difference in the frequency of angina attacks [7 10] the number of nitroglycerin tablets used for relief of angina pain [8 9] the degree of exercise tolerance [2] or exercise electrocardiogram (ECG) changes [8] One investigator reported a decreased mortality in male patients under 50 years of age with a myocardial infarct and treated with PETN [11] however he also reports no difference in mortality of male heart patients over 50 and female heart patients under 70 treated with PETN and his results indicate a higher mortality in PETN treated female patients over 70 The only report which suggests some detrimental effect of PETN treatment indicates a slight increase in shock and arrhythmias in PETN treated patients but no difference in mortality between treated and untreated patients [12]

Experimental studies of PETN action on the cardiovascular system have not elucidated its effectiveness because the results are contradictory A report of decreased mortality in PETN treated animals with coronary occlusion[13] is contradicted by reports of no decrease in mortality [3] Coronary arteriography of patients with coronary artery disease indicated PETN causes a vasodilation[14] and this is supported by reports of increased coronary flow in normal dog hearts[6] and ischemic hearts [3] However other investigators reported no change in total coronary blood flow with PETN treatment [15 16] but rather a redistribution of blood to the endocardium [15 17]

These experiments are designed to study the effect of pretreatment of dogs with PETN on clinically significant hemodynamic and metabolic parameters before and after selective coronary artery occlusion The effectiveness of PETN in ameliorating the hemodynamic and plasma biochemical changes following experimental coronary artery occlusion is examined

Methods

Experimental studies were carried out on male mongrel dogs weighing 20 to 30 kilograms The animals were anesthetized with sodium pentobarbital (30 mg per kilogram) The technique was modified from that used by Ribeilima [18] Catheters were inserted under fluoroscopic visualization as follows (1) femoral vein for measurement of pressures in the right atrium (RA) right ventricle (RV) and pulmonary artery (PA) (2) Femoral artery for measuring left atrial (LA)

From the Medical Research Department Blodgett Memorial Hospital and the Department of Biology Calvin College Grand Rapids Mich
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Reprint requests to Dr Walter D Meester Medical Research Department Blodgett Memorial Hospital 1840 Wealthy S E Grand Rapids Mich 49506

pressures and obtaining arterial blood samples (3) Jugular vein with placement in coronary sinus for withdrawing venous blood samples and injecting heparin (100 units per kilogram) and maintenance doses of anesthetic (4) Common carotid artery for measuring left ventricle (LV) and aortic (AO) pressures and also withdrawing blood for cardiac output determinations. Coronary occlusion was achieved by placing this catheter in the circumflex branch of the left coronary artery and injecting 1 1 mm diameter stainless steel ball bearings (3 per kilogram) Blood pressures were measured with a Statham P23DB pressure transducer and recorded with a Sanborn Model 150 polygraph recorder Cardiac output was measured by dye dilution using Cardiogreen dye and a Gilford 105 IR densitometer with a Lexington Instruments cardiac output computer Stroke volume was calculated from cardiac output and heart rate Vascular resistance was calculated from arterial atrial pressure difference/cardiac output and expressed as Wood units ECG was recorded using Lead II

Blood samples were drawn from the left atrium and coronary sinus for studies of enzymes blood gases acid base characteristics and metabolic substrates Standard spectrophotometric methods were used for analysis of serum glutamic oxaloacetic transaminase (SGOT)[19] lactic dehydrogenase (LDH)[20] and creatine phosphokinase (CPK)[21] The enzyme activity was expressed as international units per milliliter (IU/ml) Enzymatic methods were used for analysis of glucose[22] and lactate[23] and a titration technique for free fatty acids (FFA)[24] Blood Po_2 and pH were measured using a Radiometer pH meter Blood Pco_2 values were calculated according to the method of Astrup and co workers[25]

Protocol The experiments consisted of two groups of animals (1) myocardial infarct control group in which the left circumflex branch of the coronary artery was occluded by injection of stainless steel ball bearings and (2) the experimental group of PETN treated animals This group consisted of thirteen animals which were pretreated with 80 mg twice a day sustained action PETN* for two days before the embolization The day embolization was performed, one 80 mg

PETN supplied as P ritrate SA by Warner Chilcott Laboratories Morris Plains, N J

Table I The effect of *PETN** pretreatment on baseline hemodynamics

	Control *(n = 95)* $\overline{X} \pm S.E.$	*Peritrate* *(n = 13)* $\overline{Y} \pm S.E.$
RA	4 41 ± 0 15	5 31 ± 0 27
RV	12 43 ± 0 26	14 08† ± 0 52
PA	*19 1 ± 0 47*	*22 3† ± 1 07*
LA	7 63 ± 0 31	8 58† ± 0 37
LV	68 45 ± 1 43	76 62† ± 2 13
AO	137 84 ± 1 1	150 23† ± 3 5
CO	3 07 ± 0 09	2.83 ± 0 26
HR	156 5 ± 3 16	159 3 ± 7 1
SV	20 05 ± 0 69	17 77 ± 1 3
PVR	4 29 ± *0 17*	5 37 ± *0 73*
SVR	48 11 ± 1 58	58 16 ± 7 02

RA = right atrial pressure (mm. Hg) RV = right ventricle pressure PA = pulmonary artery pressure LA = left atrium pressure LV = left *ventricle pressure AO = aorta pressure* CO = cardiac output in L/min. HR = heart rate in beats/min SV = stroke volume in ml/stroke PVR = pulmonary vascular resistance in Wood units SVR = systemic vascular resistance in Wood units.

Pentaerythritol tetranitrate 80 mg administered orally twice a day two days prior to the day of the *experiment* and *once the morning of* the experiment.

†Indicates significant difference (P < 0 05) from corresponding control *value*

tablet was administered two hours prior to anesthesia

All hemodynamic parameters were measured and blood samples withdrawn for plasma analysis prior to embolization (base) and were repeated one two and six hours after embolization The base values were compared with corresponding values in a group (n=95) consisting of all other animals used in experimental myocardial infarction studies performed in this laboratory The data from the postembolization period was compared with the control group (n=34) The sample size is not the same for all parameters either because all parameters were not examined in each animal or particular values were excluded because of measurement errors Data were analyzed by group comparison for the calculation of *t* according to Snedecor[26] Chi square test of significance was used for analyzing the mortality data Differences between values with P < 0 05 were considered statistically significant.

Results

Effect of PETN pretreatment on base hemodynamic and plasma biochemical parameters The pre embolization metabolic and hemodynamic values of the PETN treated group

Table II Effect of PETN* pretreatment on baseline coronary sinus plasma biochemical parameters

	Control $\bar{X} \pm SE$			Peritrate $\bar{X} \pm SE$		
Po_2 (mm Hg)	30 67 ±	0 84	(56)	32 21	± 1 93	(13)
Po (mm Hg)	55 03 ±	1 79	(55)	54 26	± 4 83	(13)
pH	7 32 ±	0 008	(57)	7 336	± 0 016	(13)
Glucose (mg %)	107 23 ±	2 19	(93)	99 3†	± 3 1	(13)
Lactate (mg %)	6 0 ±	0 54	(92)	5 28	± 0 68	(13)
Free fatty acids (μEq/L)	404 7	± 22 2	(51)	416 5	± 36 9	(13)
LDH (IU/ml)	61 05 ±	4 21	(94)	28 0†	± 3 3	(13)
SGOT (IU/ml)	20 97 ±	1 60	(85)	23 9	± 2 1	(13)
CPK (IU/ml)	6 29 ±	0 37	(89)	4 81	± 0 81	(13)

Number in parentheses represents n.

Pentaerythritol tetranitrate 80 mg administered orally twice a day two days prior to the day of the experiment and once the morning of the experiment.

†Indicates significant difference (P < 0 05) from corresponding control value

were compared to corresponding values of a control group (n=95) composed of all animals used in experimental myocardial infarction studies in this laboratory As Table I indicates all pressures were significantly greater in the PETN group compared to the control group The average increase for all pressures was 13 per cent with the greatest increase observed in the right atrium The other hemodynamic parameters in the PETN treated animals reported in Table I were not significantly different from the control animals

The results of coronary sinus blood plasma analyses are shown in Table II Arterial plasma samples were also analyzed and the results were parallel to those reported here The blood gases, PO_2 and PCO_2 and pH were within normal ranges and there was no significant difference between the PETN treated and control groups The metabolic substrates analyzed showed glucose significantly lower in the PETN treated group compared to the control group and no significant difference in lactate and FFA plasma concentrations Arterial coronary sinus differences in metabolic substrates were not significantly different in the treated and untreated groups Serum enzyme analyses indicated reduced LDH levels in the PETN treated animals and no significant difference in SGOT and CPK activities.

Effect of PETN treatment on hemodynamic changes following coronary occlusion The per cent of baseline hemodynamic values at one, two and six hours following embolization of the circumflex branch of the left coronary artery are shown in Figs 1 and 2 The PETN treated group is compared to the control group in which embolization was performed but no PETN administered As Fig 1 indicates, the pressures of the PETN treated animals had lower per cent of baseline values than the control animals With the exception of right atrial pressure at one hour the values were not statistically significant. Fig 2 shows the comparison of cardiac output, heart rate and stroke volume between the PETN treated and control animals Cardiac output was not reduced as much at one hour in the PETN treated group and thus the result of a significantly smaller reduction in stroke volume in the PETN treated animals compared to the control animals Also, the PETN treated animals heart rate did not increase as much as in the control animals following coronary artery occlusion Pulmonary and systemic vascular resistance increased following embolization of the left coronary artery in the control animals this increase was less in the PETN treated animals and the pulmonary vascular resistance was actually reduced at one hour after embolization

Effect of PETN treatment on plasma biochemical parameters following coronary occlusion Fig 3 shows the results of coronary sinus plasma analyses following embolization of the circumflex branch of the left coronary artery in PETN and control animals The results are expressed as per cent of baseline values because some baseline values were not comparable due to the pretreatment of the animals with PETN The results show no statistically significant difference in Po_2, PCO_2 and pH even though Po_2 values tend to be higher and PCO_2 values lower in the PETN treated group Coronary sinus plasma glucose concentrations decreased following embolization and after six hours the glucose levels in the PETN treated group were significantly lower than the control group Arterial plasma glucose

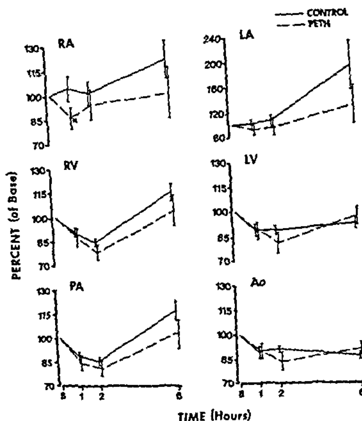


Fig 1 Mean blood pressures following embolization of the circumflex branch of the left coronary artery in a control group of dogs (n = 34) and a group pretreated with PETN (n = 8) The abscissa represents the time after embolization with B representing the pre embolization value The ordinate is the per cent of baseline value RA = right atrium RV = right ventricle PA = pulmonary artery LA = left atrium LV = left ventricle and AO = aorta An asterisk indicates a significant difference (P < 0 05) from the corresponding control value

was not decreased more in the PETN treated animals The glucose arterial coronary sinus concentration difference increased following embolization and compared to the control animals the increase tended to be greater in the PETN treated group Plasma lactate concentrations also increased after embolization There was no significant difference between the PETN treated and control animals although the lactate continued to increase in the control group whereas it reached a peak at one hour and declined in the PETN treated group FFA concentrations in coronary sinus plasma declined for one to two hours after coronary occlusion (Fig 3) but were higher than baseline after six hours and PETN had *no* statistically significant effect on FFA plasma levels or on A V concentration differences

The serum enzymes LDH SGOT and CPK all increased following embolization of the left circumflex artery The increases in LDH in the PETN treated group compared to the control group were not statistically different whereas the SGOT levels increased less in the PETN treated animals than in the control animals Baseline serum CPK levels were low in the PETN treated group however the CPK levels increased more in the PETN group than the control group

Mortality study of PETN treated and control animals with experimental coronary occlusion The summary of the mortality data is presented in Table III The sample size of PETN is small but Chi square analysis of the mortality data indicates 38 5 per cent mortality is significantly higher (P < 0 05) than the 12 5 per cent in the control animals The frequency of arrhythmias was also greater in the PETN treated group compared to the control group In the control group 21 of 40 animals had at least one arrhythmic beat in a two minute sample of the baseline record,

Table III Mortality in dogs with experimental coronary occlusion with and without PETN* treatment

	N	Deaths after embolization				Per cent mortality
		0-1 hr	1-2 hr	2-6 hr	Total	
Controls	40	1	3	1	5	12.5
PETN treated	13	3	2	0	5	38.5†

*Pentaerythritol tetranitrate administered as described in previous tables.
†Significantly different (P < 0.05) from control as determined by Chi square analysis.

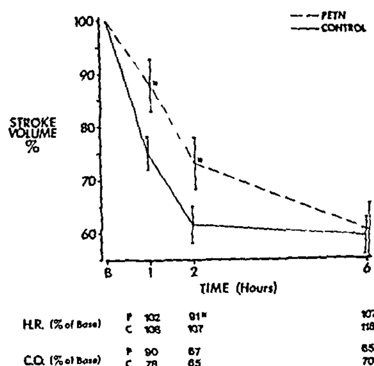


Fig 2 Stroke volume changes following embolization of the circumflex branch of the left coronary artery in a control group of dogs (n = 34) and a group pretreated with PETN (n = 8) The abscissa represents the time after embolization with B representing the pre-embolization value The ordinate represents the per cent of baseline value The numbers depicted beneath the figure represent per cent of baseline values for heart rate (HR) and cardiac output (CO) for the time following embolization listed on the abscissa An asterisk indicates a significant difference (P < 0.05) from the corresponding control value

whereas in a comparable sample period of the PETN treated animals 10 out of 13 animals exhibited arrhythmias including all five of the animals that died

Discussion

The effectiveness of nitrates in the treatment of angina and ischemic hearts has been explained on the basis of the vasodilation action of nitrates on the coronary arteries[1,2] and/or on the vasodilation of the systemic vascular system resulting in a decreased cardiac work [28] Both of these explanations have been offered for the action of glyceryl trinitrate,[2,28] however, the effectiveness and mechanism of action of the long acting pentaerythritol tetranitrate (PETN) has been debated [27] This study was designed to determine the effectiveness of PETN action on the hemodynamic and biochemical changes associated with experimental coronary occlusion by embolization of the circumflex branch of the left coronary artery

PETN was administered two days prior to embolization of the coronary artery to simulate the clinical situation where a coronary patient who is taking PETN regularly has a coronary occlusion resulting in infarction In this experiment the baseline hemodynamics measured prior to infarction indicate elevated RA RV PA, LA, LV, and AO pressures but *no significant* change in cardiac output heart rate stroke volume or peripheral vascular resistance This action and inactivity conflicts with previous reports of decreased blood pressure in patients[29] and decreased pressure in dogs[6] Others report no change in blood pressure in patients[11] or in dogs[15,31] In general, the effects on pressure seem to be small The decrease reported by Winbury, Howe, and Hefner[30] was for less than 10 minutes and in response to intravenous injection Winsor and Scott[6] reported a 6 per cent decrease in mean arterial pressure whereas a 10 per cent increase in aortic pressure is reported here Also, none of the experimental studies used pretreatment in studying the effect of PETN on hemodynamics The slightly elevated pressures in the PETN group may represent a greater compensatory response to anesthesia

The observation that PETN had no significant effect on cardiac output is consistent with the reports of its action on patients[9] and in dogs[31] However the lack of effect on vascular resistance observed here contradicts reports that peripheral vascular resistance was decreased[31] and nutritive

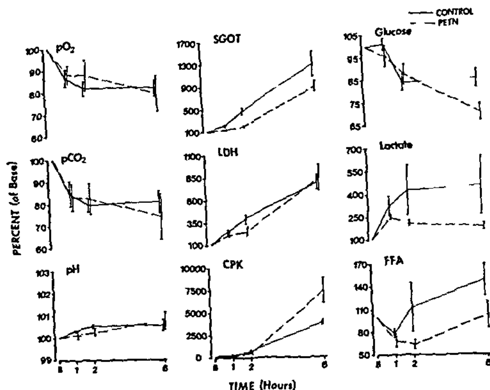


Fig 3 Plasma biochemical changes following embolization of the circumflex branch of the left coronary artery in a control group of dogs and a group pretreated with PETN (n = 8) The abscissa is the time after embolization with B representing the pre embolization value The ordinate represents the per cent of baseline value Analyses were performed on coronary sinus blood samples The key to the abbreviations is as follows with the number in parentheses representing *n* of the control group Po_2 = blood oxygen tension (21) Pco_2 = blood carbon dioxide tension (21) SGOT = glutamic oxaloacetic transaminase activity (32) LDH = lactic dehydrogenase activity (32) CPK = creatine phosphokinase activity (32) glucose = glucose concentration (32) lactate = lactate concentration (32) and FFA = free fatty acid concentration (11) An asterisk indicates a significant difference ($P < 0\ 05$) from the corresponding control values

blood flow increased[32] However in these latter two studies the drug was administered intravenously or intra arterially directly to the organ studied. So the PETN seems to have an insignificant effect on cardiac output and vascular resistance

The studies of changes in hemodynamics and plasma biochemical parameters following coronary artery occlusion by embolization of the circumflex branch indicate PETN pretreatment has no significant action The blood pressures per cent of baseline values are less than in the control group and the peripheral vascular resistance increases less in the PETN treated animals compared to the control animals The differences are not statistically significant except for the pulmonary vascular resistance value one hour after embolization This suggests that if PETN has any vasodilation activity during the six hours after embolization it is only slight. The stroke volume is decreased in the control animals with coronary occlusion however the decrease is less in the PETN treated group one and two hours after embolization This difference is statistically significant and could result from improved coronary perfusion and/or the slight decrease in pressure which reduces myocardial O_2 requirement and cardiac work

These experiments provide little evidence for improved coronary perfusion and circulation as a result of PETN treatment. Compared to the control group the changes in the blood gases Po_2 and Pco_2 are insignificant as are the changes in FFA concentration in the PETN pretreated group however glucose extraction is improved and coronary sinus lactate levels decrease in the one to six hour interval following coronary occlusion whereas the lactate increases during the same period in the control animals Previous reports indicate that PETN acts preferentially on

the large coronary arteries[30] and that this improves the flow to the endocardium Thus, even though total coronary flow does not increase the tissue Po_2 of the endocardium increases [16] Earlier reports indicated PETN treatment causes vasodilation of the coronary arteries[14] and increased coronary flow in the normal heart[6] and the ischemic heart [3] However, Uchida and coworkers[16] observed an increase in coronary blood flow in response to the initial injection of PETN, but decreases in blood flow with subsequent injections particularly following coronary occlusion

The changes in serum enzyme activity expressed as per cent of baseline values appear to be contradictory In the PETN group SGOT activity at one and two hours after embolization is less than the control whereas CPK activity at six hours is greater than the control The higher CPK per cent of baseline value is the result of a low baseline value Comparison of actual values in the PETN and control groups shows SGOT, LDH, and CPK activities less than the control following embolization These lower values suggest less myocardial damage but this cannot be verified unless total cumulative enzyme activity is measured

The effect of PETN has a very short duration even though it is supposedly a long acting nitrate [4] With sublingual administration the time to maximum action is 18 minutes [6] With intravenous injection the action persisted for 5 to 12 minutes [30 31] and with intra arterial injection blood flow increased for approximately two minutes [15] Sustained action preparations of PETN have metabolic products which have peak concentrations four to eight hours after oral administration [33] but whether or not these products are active is unknown The effectiveness of PETN as a long acting nitrate has also been disputed in clinical studies [2] Our results also indicate that PETN has no significant effect after one or two hours

The most striking effect of PETN treatment in this study is that mortality of PETN treated animals was 38 5 per cent compared to 12 5 per cent in the control animals Even though the sample of PETN treated animals was small, the difference in mortality was significant at the 0 05 level of confidence On the basis of the hemodynamic and biochemical parameters measured in this study, there is no good explanation for the higher mortality Examination of the ECG's, however, indicates a higher incidence of arrhythmias in the PETN treated animals compared to the control animals All five of the animals that died had some arrhythmia prior to experimental coronary occlusion Previous mortality studies give conflicting reports Lumb and Hardy[13] reported PETN treatment resulted in a significant decrease in mortality in pigs with coronary occlusion whereas Leighninger, Rueger and Beck[3] reported no decrease in mortality or in infarct size The increased mortality with PETN reported here may be the result of using relatively high doses of PETN compared to clinical studies The PETN dosage used was twice that used by Winsor and Scott,[6] but is less than one fifth of the dosage used by Winbury and coworkers [17] who claim that lower doses are ineffective The PETN treatment does not seem to alter the hemodynamic or metabolic parameters enough to explain the higher mortality The increased mortality may be related to the higher incidence of arrhythmias

Summary

The present investigation indicates that PETN treatment (1) results in a slight increase in mean blood pressures but has little or no effect on other hemodynamic or plasma biochemical parameters (2) slightly improves hemodynamic parameters following coronary occlusion (3) increases glucose extraction by myocardium and lowers lactate levels which suggests some improved metabolism, and (4) results in increased mortality following coronary occlusion

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Pulmonary arterial pressure method for estimating the ventricular stroke volume

Anthony A Cibulski M D, B E E*
Patrick H Lehan, M D
Seshadri Raju, M D
Thomas L Keister Jr, B S
Kenneth R Bennett, M D
Harper K Hellems, M D
Jackson Miss

Surveillance of the pulmonary arterial (PA) and capillary wedge (PCW) pressures in coronary care units has been widely accepted as a safe and valuable procedure in the clinical management of acute myocardial infarction[1,2] The PA and PCW pressures provide a reasonable index of the left ventricular performance and serve as a useful guide in the therapeutic management of the patient Work was undertaken for this report to determine if additional useful information could be derived from these measurements with a pulmonary arterial pressure method for estimating the right ventricular stroke volume

Methods

The data to be reported were collected in experiments with five mongrel dogs ranging in weight from 22 to 28 kilograms All animals were anesthetized with an initial dose of intramuscular morphine (0 5 mg per kilogram of body weight) and intravenous pentobarbital (30 mg per kilogram of body weight) and secured in the right lateral decubitus position Right and left heart catheterization was performed under fluoroscopic control with the following procedures (1) a No 7 Goodale Lubin catheter was inserted via the left jugular vein and advanced to the pulmonary artery (PA), (2) a No 7 Eppendorf catheter was advanced from the left carotid artery to the aortic root All catheters were periodically flushed with heparinized saline (01 mg of heparin per 1 c c of saline) A left thoracotomy was performed at the fourth intercostal space The main PA was dissected free for implantment of a Statham a c electromagnetic flow transducer which was connected to a Statham flowmeter A sine wave generating pump was employed to obtain an in vitro calibration of the flow transducer The PA and aortic root catheters were connected to Statham strain gauge transducers The frequency response characteristics of the catheter pressure transducer recording system showed resonant frequencies between 30 to 40 Hz. Pulsatile pulmonary flow and pressure were recorded with the Electronics for Medicine recorder with paper speeds of 100 mm per second and 02 second time lines All heart beats recorded for study were obtained during the resting end expiratory phase of respiration in order to (1) eliminate pressure artifacts resulting from mechanical disturbances of the PA catheter during inspiration and (2) eliminate potential variables resulting from alterations of the pulmonary vascular anatomy which occurs between the extremes of the respiratory cycle The ECG was monitored continuously throughout the experiment

At the beginning of each experiment the PCW pressure was employed as an estimate of the left atrial pressure and was recorded in rapid sequence with the PA pressure under baseline con

From the Department of Medicine University of Mississippi Medical Center 2500 North State St Jackson Miss

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Reprint requests to Anthony A Cibulski M D University of Mississippi Medical Center 2500 North State St Jackson Miss 39216

Present address Cibulski Fawal and Maloof Pa 8010 2nd Ave South Birmingham Ala 35206

ditions This was accomplished by advancing the PA catheter to the PCW position to record the mean PCW pressure for 5 to 10 seconds The respirator was turned off in the end expiratory phase of respiration during the period of recording Immediately after the PCW pressure was recorded the catheter was withdrawn to the main PA to record pulsatile pressure The pulsatile PA and mean PCW pressures were superimposed as shown in Fig 1 and the areas enclosed between these pressures during systole and diastole were defined as A_{so} and A_{do} respectively These area measurements were made by planimetry and were used in the stroke volume formula described in the following section

The principles of the pulmonary pressure method (PPM) for estimating stroke volume (SV) are presented in the discussion section The formula for stroke volume is

$$SV = K(A_p + q\sqrt{\Delta P_d})$$

where K is a calibration constant A_p is the shaded area shown in Fig 1 which is enclosed by the systolic pressure and a straight line drawn from the pulse base to the pressure at the onset of diastole ΔP_d is the difference between the diastolic maximum and minimum pressure The diastolic maximum was determined by extrapolating the diastolic pressure curve backward to intersect a vertical line passing through the incisura of the dicrotic notch as illustrated in Fig 1 The term q was equated to $(A_{po}/\sqrt{\Delta P_{do}})(A_{do}/A_{so})$ and was employed as a constant in the formula for stroke volume The component terms of q were determined from the superimposed baseline PA and PCW pressures which were recorded in rapid sequence at the beginning of the experiment The baseline measurement of stroke volume by the PPM was equated to the corresponding flowmeter measurement of stroke volume (i e the planimeterized area under the flow pulse recorded simultaneously with the baseline PA pressure) and K was determined. This value of K was used in the PPM throughout the remainder of the experiment.

Simultaneous measurements of stroke volume were obtained with the flowmeter and pressure methods under the following conditions

1 Premature ventricular contractions were induced by manipulating a 23 gauge needle over the exposed myocardial surface The stroke volumes of the extrasystolic (20 to 55 per cent of control measurements) and first post extrasystolic contractions (125 to 170 per cent of control measurements) were measured.

2 Right ventricular epicardial pacing was established with a Grass S4 simulator Heart rates ranged from 102 to 160 beats per minute

3 Epinephrine in saline solution was infused at rates of 1 to 2 μg per minute to achieve heart rates of 150 to 180 beats per minute or mean systemic pressures of 120 to 180 mm Hg

4 Isoproterenol in saline solution was infused at rates of 1 to 2 μg per minute to achieve heart rates of 150 to 180 beats per minute

5 The animal was bled in 50 to 100 c c increments to reduce the stroke volume to approximately 50 per cent of control measurements

All drugs were administered intravenously and 5 to 10 minute recovery periods were allowed between each intervention

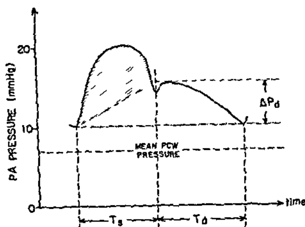


Fig 1 The pulsatile pulmonary artery (PA) and mean capillary wedge (PCW) pressures are here shown superimposed. PA = pulmonary artery PCW = pulmonary capillary wedge ΔP_d = difference between the diastolic maximum and minimum pressures (mm Hg) T_s = duration of systole (second) T_d = duration of diastole (second)

Results

The results of the PPM and flowmeter method (FMM) for determining the right ventricular stroke volume are compared in Table I for all interventions in the individual dog and for all dogs with the various interventions considered separately The interventions employed in this study produced a wide variation in the flowmeter measurement of stroke volume (2 7 to 22 0 c c) mean aortic pressure (55 to 170 mm Hg) and mean PA pressure (13 to 34 mm Hg) The stroke volume in each dog ranged from 20 to 170% of

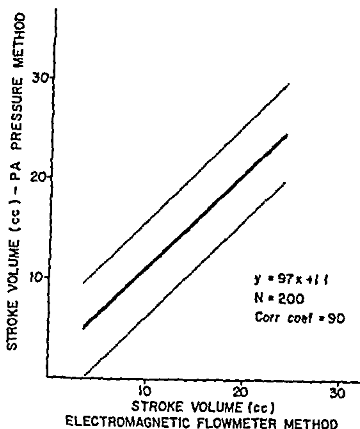


Fig 2 The solid line represents the regression equation y = 97x + 1 1 c c which describes the relationship between 200 determinations of stroke volume by the electromagnetic flowmeter and pulmonary pressure (PPM) methods The 200 comparison points were obtained in studies with 5 dogs in which various interventions produced a wide variation in stroke volume The dashed lines indicate the 95 per cent confidence limits of the mean PPM estimate (i e ± 1 96 × the standard error of the PPM estimate)

control values In Fig 2 the over all relationship between 200 comparison measurements of stroke volume by the PPM and FMM is presented as a straight line regression equation, y = 97x + 1 1 c c , with a correlation coefficient of 90 The standard error of the mean stroke volume estimate by the PPM was 17 7 per cent

Discussion

In a previous report[3] an arterial pressure method for computing the ventricular stroke volume was developed from principles describing the passage of a flow pulse through the arterial vessels during systole The stroke volume formula derived in this manner is

$$SV = KA_p(1 + A_d/A_s) \qquad (1)$$

where KA_p is interpreted to be the systolic outflow of the central arterial vessels

The basic Warner formula[4] for stroke volume was found on the premise that the central arterial vessels undergo passive decompression during diastole and it is summarized below

$$SV = C\Delta P_d(1 + A_s/A_d) \qquad (2)$$

where C is a calibration constant and $C\,\Delta P_d$ is the diastolic outflow of the central arterial vessels The detailed derivation and empirical modifications of equation 2 are given in the reference cited above

Stroke volume may also be expressed as the sum of the systolic and diastolic outflows from the arterial channels For example

$$SV = KA_p + C\Delta P_d \qquad (3)$$

A relationship between K and C is found by equating the stroke volumes of equations 1 and 2 and rearranging terms to express C/K as $(A_p/\Delta P_d)$ (A_d/A_s) or simply q Substitution of qK for C in equation 3 yields $SV = K(A_p + q\Delta P_d)$ This latter expression for stroke volume was modified, on an empirical basis to the form shown in equation 4 in order to achieve closer comparison measurements of stroke volume with the electromagnetic flowmeter method (FMM)

$$SV = K(A_p + q\sqrt{\Delta P_d}) \qquad (4)$$

where q is redefined as $(A_{po}/\sqrt{\Delta P_d})$ (A_{do}/A_{so}) The component terms in q are initial baseline measurements

At the beginning of each experiment K and q were determined under baseline conditions and assumed to be invariable throughout the remainder of the experiment The manner in which these terms may vary under changing hemodynamic conditions is seen by examining their variable physiologic components. For example $K = g\pi R/\rho c$ where g is the gravitational constant ρ is the blood density, R is interpreted to be the end diastolic radius of the vascular bed considered as a uniform channel of length L c is the average velocity of a pulse passing through the system[3,5] The term C (i e the arterial pulse volume – pulse pressure) is $g\,V/\rho c^2 = g\,L\pi R^2/\rho c^2$ where V is the end diastolic volume of the arterial bed[6] For simplicity the anatomic dimensions described in the terms C and K are considered to be in a fixed proportion to each other under varying physiologic conditions On the basis of this assumption the proportion C/K (i e q) is $\lambda L/c$ where λ is a constant of proportionality

The overall reliability of the pulmonary pressure method (PPM) for estimating stroke

Table I Comparison of stroke volume measurements by the PA pressure and electromagnetic flowmeter methods

					Stroke volume			
Intervention	*N*	*r*	*b*	*c* *(mL)*	*FMM* *Mean (range)* *(mL)*	*PPM* *Mean* *(mL)*	*SE (PPM)* *(mL)*	*% SE (PPM)*
PVC + 1st post PVC beat	40	95	1 05	− 5	10 9 (2 7 22 0)	11 0	2 1	19 1
Ventricular pacing	40	94	97	− 2	9 8 (6 4 11 2)	9 3	4	4 3
Epinephrine	40	81	77	6 6	13 6 (8 9 18 8)	17 1	1 4	8 2
Isoproterenol	40	87	93	7	13 1 (9 1 17 4)	12 9	1 1	8 6
Hemorrhage	40	90	99	9	10 5 (6 9 12 6)	11 3	6	5 3

						Stroke volume			
Dog	*Weight* *(Kg)*	*N*	*r*	*b*	*c* *(mL)*	*FMM* *Mean (range)* *(mL)*	*PPM* *Mean* *(mL)*	*SE (PPM)* *(mL)*	*% SE (PPM)*
1	22	40	93	97	8	10 2 (2 7 18 2)	10 7	1 3	12 1
2	23	40	90	98	1 0	10 5 (3 0 19 5)	11.3	1 6	14 2
3	23	40	89	95	1 3	12 4 (3 3 21 1)	13 1	1 7	13 0
4	26	40	87	92	2 1	11 8 (2 9 19 8)	12 9	1.9	14 7
5	28	40	93	99	7	13 0 (4 1 22 0)	13 6	1 5	11 0
All	24 4	200	90	97	1 1	11 6 (2 7 22 0)	12 3	2 4	17 7

Abbreviat ons *N* = numbe of observ t ns r = correlation coefficient b = slope c = intercept PPM and FMM = stroke volume st mates by the pul monary a teri l (PA) pressure and electromagnetic flowmeter m thods respectiv ly SE (PPM) = standard erro of the stroke volume estimat on by th PA pressure method % SE (PPM) = (SE (PPM) / mean PPM) × 100 PVC = premature entri ular cont action

volume (Table I) suggests the factors R^2/c in K and L/c in q may not vary substantially over a wide range of physiologic conditions Inaccuracies of the PPM during the epinephrine intervention may be ascribed to alterations in one or both of these factors. The hypothetical dimensions R and L are interpreted to be the average values of a uniform vascular channel simulating the pulmonary vascular bed and therefore are not subject to direct measurement. If L may be considered as a virtual constant then q is inversely proportional to c It has been well established that the wave velocity through the various aortic segments increases with the mean intraluminal pressure in a nearly linear fashion[6,9] The behavior of the wave velocity and pressure in the pulmonary bed has not been clearly defined with direct experimental measurement however Bargainer[14] has shown that the wave velocity through the main pulmonary artery of the dog increases with pressure Kouchoukos and colleagues[5] have suggested that the R^2/c factor of the systemic arterial bed may be reasonably constant if both R^2 and c vary proportionately over a wide range of intraluminal pressures Data supporting this argument for the pulmonary bed is not available

As mentioned earlier c is the average velocity of a pulse passing through the pulmonary bed considered as a uniform channel Although c cannot be measured directly a stroke volume formula in which c is considered as a variable may be developed in the form of equation 5 shown in the Appendix The performance of equation 5 (reported in Appendix) for predicting the FMM measurement of stroke volume may be compared against the corresponding performance of equation 4 (reported in Table I) in order to roughly assess the magnitude of error which occurs when c is approximated as a constant Comparison of these pressure methods suggests that when c is considered as a variable a definite improvement in accuracy is achieved during the epinephrine intervention whereas little or no improvement is gained during other interventions

The format of equation 4 offers the advantages

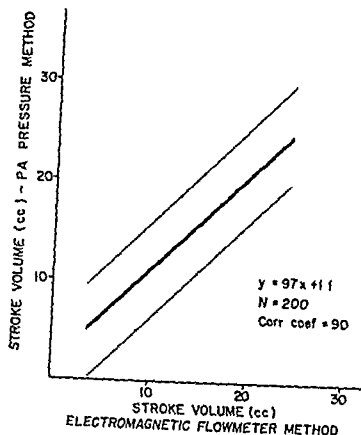


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The overall reliability of the pulmonary pressure method (PPM) for estimating stroke

Effect of exercise on myocardial infarction in young vs old male rats electrocardiograph changes

Bernard C Wexler Ph D *
Bruce P Greenberg Ph D **
Cincinnati, Ohio

Death due to myocardial infarction is reaching epidemic proportions and its age of onset is no longer confined to the elderly but is now affecting young adults in ever increasing numbers The course of pathophysiologic events which attend an acute myocardial infarct in young vs old adults is rather disparate Currently there is considerable emphasis on the salutary effects of exercise on myocardial performance However more fundamental information is needed to determine whether the salutary effects of exercise are real or imagined and whether there may be a different response to exercise in the young vs old ischemic heart

For the past several years we have been investigating the induction of acute myocardial infarction in rats by means of the potent beta adrenergic stimulating agent isoproterenol [1-3] The pathophysiologic changes in these animals during the acute phases of myocardial necrosis and repair mimic those which occur in patients, i e changes in serum enzymes lipids catechol amines steroids etc In earlier investigations we had demonstrated definite electrocardiogram (ECG) evidence of myocardial ischemia in isoproterenol treated rats [4] Using our ECG methodology as objective evidence of myocardial responsiveness we subjected both young and old rats to an isoproterenol induced myocardial infarction By regulating the dose of isoproterenol we can produce myocardial infarctions of comparative equal size and severity in both young and old rats. Some of the young and old subjects were exercised by forced swimming for two weeks prior to the induction of infarction Our purpose was to determine by ECG tracing if young and old rats would differ in their response to acute myocardial ischemia and whether exercise would have similar salutary effects on young vs old hearts

Materials and methods

A total of 400 adult male Sprague Dawley rats were used in these investigations 200 young males 90 days of age weighing 310 to 350 grams and 200 old males 15 months of age weighing 500 to 580 grams *

Prior to exercise (Day 0) the electrocardiogram of half of each group of animals was recorded These animals served as controls and as a baseline for subsequent studies of the ECG changes during both the course of repeated daily exercise and the temporal development of acute myocardial ischemia necrosis and repair Rats were individually immersed in large glass chambers filled with water (32 C) which was carefully monitored and controlled to avoid environmental or physical stress factors The animals were forced to swim for a standard period of time (30

From the May Institute for Medical Research of the Jewish Hospital of Cincinnati, Cincinnati And the Department of Medicine Pathology and Pharmacology University of Cincinnati College of Medicine Cincinnati.

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Reprint requests to Dr B C Wexler May Institute for Medical Research, 421 Ridgeway A Cincinnati, Ohio 4 9

* Associate Professor of Experimental Medicine and Pathology Director May Institute

** Assistant Professor of Clinical Pharmacology Research Associate May Institute

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of technical simplicity in the graphical solution of stroke volume by the PPM For example, only a single initial estimate of the left atrial pressure by the pulmonary capillary wedge technique was obtained for the computation of q at the beginning of each experiment All subsequent measurements required for the solution of stroke volume were taken from the pulse pressure itself without further reference to the pulmonary venous outflow pressure The reliability of this approach depends upon the constancy of q as mentioned earlier The protocol of other pressure methods[4 5 11] presently described in the literature requires nearly equal diastolic pressures at the onset and termination of the pulse chosen for study and are therefore dependent upon the timing of the subsequent heart beat The method described here is independent of the diastolic period and may therefore be applied in the presence of persistent ventricular arrhythmias

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Appendix

A theoretical approach for estimating directional changes in the average wave velocity of the pulmonary bed is found by relating the arterial hemodynamic events which distinguish systole from diastole For example the variables describing the transmission of a flow pulse through the arterial channels during systole are related in the text to the variables describing the *passive decompression of the arterial vessels* during diastole by combining equations 1 and 2 to obtain $C/K = (A_p/\Delta P_d)\,(A_d/A_s)$ which also equals $\lambda L/c$. Rearranging terms $c = (\lambda L)\,(\Delta P_d/A_p)\,(A_s/A_d)$ A formula for stroke volume in which c is considered as a variable is obtained by substituting the latter form of c into K (i e , $g\pi R^2/\rho c$) of equation 1 to yield $SV = K A^2{}_p (A_d/A_s\Delta P_d)(1 + A_d/A_s)$ *where* $K = g\pi R^2/\rho\lambda L$ This equation was modified on an empirical basis, to the form shown in equation 5 in order to achieve closer comparison measurements with the FMM for estimating stroke volume

$$SV = K A_p \sqrt{(A_d/A_s\Delta P_d)(1 + A_d/A_s)} \qquad (5)$$

In equation 5 A_s and A_d were equated to the areas enclosed between a horizontal baseline drawn at the estimated left atrial pressure (i e, 5 mm Hg) and the pulmonary artery pressure during systole and diastole respectively Statistical comparison of stroke volume measurements by equation 5 and the FMM are summarized as follows

(1) ventricular pacing, N = 40, y = 95x + 3 ml, r = 93 % SE = 4 8

(2) epinephrine, N = 40, y = 96x + 2 1 ml r = 94 % SE = 5 1

(3) isoproterenol N = 40, y = 93x + 4 ml r = 91, % SE = 7 6,

(4) hemorrhage N = 40 y = 86x + 2 1 ml, r = 84, % SE = 8 9

Statistical analysis of the ECG data was performed using Student's t test and statistical tables recommended by Snedecor and Cochran[6]

Results

General observations Both the young and old male animals responded to the myocardial infarction inducing effects of isoproterenol in a characteristic manner Immediately following the first injection of isoproterenol all of the animals became prostrate stuporous, and anuric Although the anuria persisted the animals began to move about after 12 hours. The young nonexercised animals appeared to withstand the duress of acute myocardial infarction better than their older counterparts i e less severe signs of heart failure and shock and a greater number of survivors The same syndrome of anuria and prostration was promptly re established after the second injection of isoproterenol The mortality rate was particularly high following the second injection of isoproterenol on D2 when myocardial necrosis became fully established By D3 the survivors manifested severe myocardial infarction By the seventh day (D7) however myocardial injury became greatly resolved so that there was little gross or histologic evidence of the antecedent severe myocardial necrosis The details of the acute onset and repair of an isoproterenol induced myocardial infarction have been described.[1,3]

Changes in heart weight The average body weight of the 15 month old males ranged from 150 to 200 grams more than their young male counterparts The hearts of the older rats were also substantially heavier than those of the young male rats The absolute weight (as well as the ratio of heart weight to body weight) of the young and old male rats showed a prompt and statistically significant increase four hours after the first injection of isoproterenol (Fig 1)* The heart weights of the young males continued to rise considerably with a peak increase eight hours after the first injection of isoproterenol the changes in the heart weights of the older males was also quite marked but not as intense as in the younger subjects

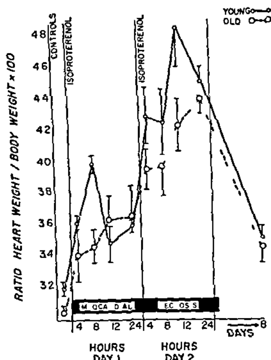


Fig 1 Changes in the ratio of heart weight/body weight (mean ± standard error) of young and old male rats at various time intervals after two injections of isoproterenol spaced 24 hours apart Myocardial necrosis is an on going event and becomes maximal between the second and third day Myocardial repair is rapid and occurs between the fourth to twelfth day

Following the second injection of isoproterenol the hearts of both the young and old rats continued to increase in weight Again the young rats showed the most sustained and the greatest increase in heart weight following the second injection of isoproterenol After seven days although gross and histopathologic evidence indicated that the heart damage was essentially completely repaired the weight of the hearts of both the young and old rats was still above normal Exercised rats showed the same pattern of change in absolute heart weight following isoproterenol as the nonexercised rats After exercise the absolute weight of both the young and old rats was increased 1 25 times

Serum enzyme changes Changes in serum enzyme levels can be used as a sensitive index of the extent or severity of an isoproterenol induced myocardial infarction[1,3] The older rats displayed the same enzyme changes as their younger counterparts with slightly lower peak values Exercise did not appreciably alter the degree of enzyme changes in the young or old rats

Electrocardiographic data Serial ECG tracings

* Rats subjected to isoproterenol induced myocardial infarction manifest an increase in both wet and lipid free dry weight reaching a peak on the third day with gradual return to normal by the seventh day (Judd, J T and Wexler B C Myocardial Connective Tissue Metabolism in Response to Injury Circ Res 25:201 1969)

Table I Electrocardiographic data from young and old, exercised and nonexercised, male rats during the course (seven days) of isoproterenol induced myocardial infarction

		D0	$D0_e$	D1	D2	D3	D7
Before exercise							
Heart rate	O M	290 2 ± 7 1		479 8 ±10 9	533 1 ±11 9	522 5 ±10 1	353 7 ±12 1
(beats/min.)	Y M	316 7 ±12 3		509 8 ±17 9	640 2 ±10 9	567 0 ± 9 0	334 1 ± 9 8
R wave	O M	0 36± 0 03		0 34± 0 04	0 26± 0 03	0 22± 0 04	0 11± 0 02
(mv)	Y M	0 43± 0 03		0 18± 0 05	0 08± 0 02	0 19± 0 03	0.23± 0 04
Q wave	O M	0 0		0 0	37 0	14 0	60 0
(%)	Y M	0 0		20 0	50 0	60 0	40 0
After exercise							
Heart rate	O M	272 6 ± 6 2	302 2 ±9 0	462 8 ± 7 6	513 8 ±11 0	509 0 ± 6 0	342 2 ± 6 9
(beats/min)	Y M	323 9 ± 9 2	339 8 ±5 0	519 0 ±10 8	618 8 ±12 7	541 5 ±12 9	359 9 ±11 3
R wave	O M	0 38± 0 02	0 37±0 02	0 31± 0 02	0 18± 0 03	0 23± 0 03	0 17± 0 04
(mv)	Y M	0 43± 0 02	0 47±0 02	0 17± 0 03	0 15± 0 03	0 34± 0 03	0 30± 0 03
Q wave	O M	0 0	0 0	0 0	10 0	9 0	20 0
(%)	Y M	0 0	0 0	30 0	40 0	31 0	23 0

Each value represents the mean ± standard error of 25 animals.

minutes) After swimming, the rats were dried and replaced in their cages This procedure was repeated daily for two weeks

Following two weeks of exercise (Day 0_e), the electrocardiogram of each animal was recorded again These animals also served as 'controls' and as a baseline for subsequent studies of those ECG changes which might occur during the course of acute myocardial ischemia, necrosis and repair Both young and old exercised and nonexercised, rats were injected subcutaneously with 50 mg per 100 grams of body weight of isoproterenol and four hours later their ECG's were recorded This was designated as Day 1 (D1) Twenty four hours later the second injection of isoproterenol was given to the remaining animals and again their ECG was recorded four hours after injection This was designated as Day 2 (D2) On Day 3 (D3) approximately 24 hours after the last injection of isoproterenol, ECG's were recorded and 50 per cent of the remaining animals were killed On the seventh day (D7), after the initial injection of isoproterenol ECG s were recorded and the remainder of the animals were killed

To obtain sequential information on the temporal progression of the pathophysiologic changes relative to the progressive onset and repair of the myocardial necrosis young and old nonexercised rats were killed by exsanguination, (syringe inserted into the abdominal aorta and blood withdrawn) at 4 8, 12 and 24 hours after both the first and second injections of isoproterenol, as well as seven days following the first injection of isoproterenol Blood collected in this manner was centrifuged under refrigeration and frozen until time for analysis Serum creatine phosphokinase (CPK) transaminases (SGOT and SGPT), and lactic dehydrogenase (LDH) were analyzed by means of Auto Analyzer (Technicon)

ECG's were recorded with the animals in a supine position using a combination of sodium secobarbital (Seconal) and light ether anesthesia ECG needle electrodes were placed subcutaneously in all four limbs and a small electrical crocodile clip was used as the chest electrode The six standard limb leads as well as the three precordial leads (VA, VB, and VC) were recorded with a Sanborn 296 twin channel direct writer (frequency response down 3 db at 100 c p s), at a paper speed of 100 mm per second VA was recorded from the right of the sternum in the area of V_1 while both VB (area of V_2) and VC (areas of V_4 and V_5) were recorded from the left of the sternum Sensitivity was adjusted so that 1 mv was equal to a 1 cm deflection The amplitudes of the R wave and J point were estimated to the nearest 0 1 mv but the means and standard errors for each group are reported to the nearest 0 01 mv Q wave per cent represents the number of Q waves seen in L2 each day in individual tracings of rats in each group relative to the total number of ECG s recorded for the group on the day (Table I) Only those animals which survived to D3 were used in the computations

tration of isoproterenol Of particular interest is the fact that only the older male rats demonstrated any ameliorative effects of exercise on the acute pathophysiologic course of their myocardial infarction Cardiologists are well aware of the fact that heart disease differs considerably in young vs elderly patients. For example, just as skeletal muscular power and pulmonary function begin to fail with age so does cardiac output[6] there is increased vagal tone bradycardia and an altered heart rate in response to exercise[7] the syndrome of acute myocardial ischemia is different in old vs young victims e g less pain but more dyspnea and congestive heart failure in the elderly[8] and there is a greater incidence of ventricular aneurysm formation and rupture in the aged.[9] The frequent absence of pain during acute myocardial ischemia in the elderly is attributed to changes in pain receptors and the development of extensive collateral circulation in the heart in response to many years of progressively worsening arteriosclerosis Despite the untoward progressive degenerative changes in the heart which occur with age there is clinical and electrocardiographic evidence that older subjects will show ameliorative changes of their ischemic heart disease with exercise and increased physical fitness which stimulates increased coronary collateral circulation[10 11] Similar age related differences in cardiac performance have been reported in experimental animals For example Shreiner Weisfeldt and Shock[12] found that cardiac performance becomes impaired in older male rats because of progressive left ventricular dilation heart rate decreases[13] blood pressure increases[14] and the electrocardiogram shows an increased incidence of arrhythmia and left axis deviation and prolongation of the P R and QRS intervals[13 15 16] Rakusan and Poupa[17] noted an increased fiber to capillary ratio in older rats which would imply a greater area of sarcoplasm to be perfused by coronary flow However Grodner Pool and Braunwald[18] believe that cardiac contractile force does not deteriorate with age in the rat since they found that length tension relationships velocity of shortening maximum isometric tension maximum rate of force development, and the time to peak tension of right ventricular papillary muscle did not diminish with advancing age

The effect of exercise on *myocardial* performance The fact that only the older subjects in our experiments manifested improved resistance to isoproterenol induced myocardial ischemia is particularly provocative The possible relationship of exercise to benefit myocardial hypertrophy increased coronary arterial blood flow and collateralization and serum enzyme changes in both the young and the old is of great clinical import because of the ever increasing incidence of heart disease In assessing the pros and cons of exercise on heart disease the parameters of myocardial hypertrophy coronary arterial flow and increased coronary artery collaterals must be kept separate in consideration

Increased coronary artery blood flow and collateralization Clinical experience demonstrates that the stress of exercise will help delineate normal patients from those with impaired cardiac function[19 20] but some cardiologists claim that the presence of coronary collaterals does not improve cardiac function in response to exercise[19 21] These investigators contend that although increased collaterals may carry more blood it is doubtful whether they can carry the extra blood required to meet a real increase in myocardial oxygen demand, e g angina myocardial infarction and hemodynamic or ventriculographic abnormalities However Knoebel and co workers[22] found that coronary bridge collaterals will manifest a protective effect when patients are challenged with the stress of injected isoproterenol Because of the extremely complex nature of the coronary arterial system of the rat it would be hazardous to claim extra collateral growth in the hearts of our old rats in response to exercise to account for their improved performance However Bloor Pasyk and Leon[23] and Leon and Bloor[24] claim that exercised rats increase the cross sectional area of their coronary arteries Tomanek[25] also claims that exercised rats exhibit an increased myocardial perfusion because of an increased capillary to fiber ratio but that this latter positive change is age dependent and Stevenson and co workers[26] using a special coronary vinyl acetate cast technique claim that swimming will cause an increase in the distribution of the coronary arteries in the rat. Weisfeldt and co workers[27] contend that old male rats exhibit lower coronary blood flow than their younger counterparts when challenged with severe hypoxia indicating that old hypoxic rats are unable to compensate for myocardial hypoxia by adjustments in coronary blood flow i e

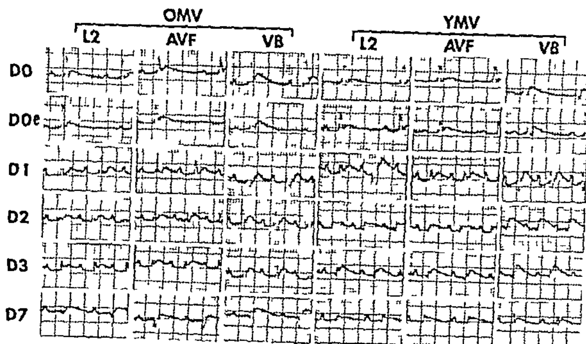


Fig 2 Electrocardiographic recordings from young (YMV) and old (OMV) male virgin rats before exercise (D0) after exercise ($D0_e$) and during (D1 D2 D3 and after D7) isoproterenol induced myocardial infarction

showed that young and old male virgin rats given two injections of isoproterenol 24 hours apart, exhibit definite evidence of myocardial infarction These ECG alterations comprise a pattern consisting of the appearance of Q waves not present in the control animals (Fig 2 YNV D2 D3 and D7) elevation of the J point above the control level (Fig 2, OMV L2 and aV_F on D3), reduction in the amplitude on the R wave (Fig 2, OMV L2 on D0 through D7) tachycardia and ventricular arrhythmias These ECG abnormalities correlate with the histopathologic evidence of progressive myocardial necrosis

Ancillary control experiments with isoproterenol demonstrated that the young males manifest ECG alterations earlier than their old male counterparts (Table I) The young males exhibited a greater reduction in R wave amplitude a larger percentage of Q waves and more elevated J points after both one or two injections of isoproterenol In addition, the heart rate of the young males on both D2 and D3 was significantly greater ($p < 0.005$) than that in the old males Forty per cent of the young rats died after two injections of isoproterenol, 50 per cent of the old males succumbed.

Although young and old rats were exercised by swimming for one half hour daily for two weeks the ECG's of the exercised controls ($D0_e$) were not significantly different from the ECG's of the control animals before exercise (Fig 2, D0 vs $D0_e$)

The ECG patterns of the isoproterenol treated, exercised and nonexercised, young subjects was essentially the same There were no statistically significant differences in the mortality rates heart rate, Q wave percentage J point level or the R wave (with the exception of D2 where the R wave was significantly lower [$p < 0.001$]) of the nonexercised young males

The exercised old males responded less drastically to the untoward effects of acute myocardial ischemia than their nonexercised counterparts. Survival was increased from 50 to 65 per cent and ECG s recorded from the exercised old males showed a reduction in the percentage of Q waves appearing in L2 on D2, D3, and D7 (Table I) Frequently, Q waves were not seen in L2 until D7 (Fig 2 OMV D7) There was also a reduction in the incidence of ventricular arrhythmia in the ECG s of the exercised old males after isoproterenol The heart rate J point location and R wave reduction in the exercised old males were not significantly different from the pre exercised values on D1, D2, D3 and D7 (Table I)

Discussion

Myocardial performance as related to age—general These results demonstrate that young and old rats show pathophysiologic as well as electrocardiographic evidence of the successful production of a "syndrome of acute myocardial ischemia and infarction following the adminis

of the alleged superior response of younger hearts to exercise Our work suggests that it is not too late at least in rats for exercise to have salutary effects on myocardial performance in older subjects

Exercise and electrocardiographic changes The significance of increased heart size in old rats in response to submaximal exercise may be problematical the possibility of the development and functional capacity of increased coronary arterial flow and collateralization may be enigmatic but the serum enzyme changes along with improved survival and positive ECG findings provide objective information of a real beneficial effect of exercise As indicated earlier other investigators have demonstrated that older rats manifest an increased incidence of arrhythmias left axis deviation and prolongation of the P R and QRS intervals [13 15 16] Despite the above detrimental criteria in older rats the ECG s recorded from our old rats during the course of their acute infarction exhibited a delayed onset of any abnormal ECG signs reduction in the percentage of Q waves present on D2 D3 and D7, and a decline in the incidence of ventricular arrhythmia Young rats after exercise showed no improvement in their ECG pattern as well as no improvement in their survival rate during isoproterenol induced infarction and at the same time showed the earliest ECG evidence of myocardial ischemia i e within 24 hours after the first injection of isoproterenol and the appearance of Q waves (L2) on D2 and D3 and the reduction in R wave amplitude on D1 D2 and D3 with return to normal on D7 and tachycardia on D1 D2 and D3 (The electrocardiographic evidence of infarction in these animals is based upon the appearance of Q waves the elevation of the J point reduction in the amplitude of the R wave, and ventricular arrhythmias.) Details concerning these ECG parameters have been published.[4]

Summary

Young (90 days) and old (15 months) male Sprague Dawley rats were either exercised (forced swimming) daily for two weeks or allowed to remain naturally active (young) or sedentary (old) Two subcutaneous injections of the potent beta adrenergic stimulating agent, isoproterenol were given to induce acute myocardial ischemia and infarction in both the exercised and nonexercised, young and old rats Exercise improved the survival capacity of the old but not of the young rats In addition the exercised old rats manifested cardiac hypertrophy reduced excursion of serum enzymes indicative of myocardial necrosis and their ECG tracings demonstrated less evidence of arrhythmias or extensive myocardial infarction

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the coronary bed cannot increase in proportion to the ventricular mass. It would seem reasonable to conclude within the context of our experiments, that since the young male rats were, by nature, extremely active, the additional exercise they received, i e, forced swimming, did not enhance their cardiac performance capacity whereas the old male rats were responsive to the exercise because of their change from a comparatively much more sedentary activity to a more active state and, hypothetically, to an increase in coronary artery function—if the aforementioned investigations are correct

Exercise serum enzymes and myocardial ischemia It is of interest that changes in serum enzymes, e g, CPK, LDH, SGOT, and SGPT, indicative of myocardial ischemia occurred earlier in the young male rats concomitant with their equally early abnormal ECG tracings It is also of interest that the physical stress of exercise *per se* did not increase the serum enzyme levels in either the young or old rats Wolfson and coworkers[20] have shown that even sedentary patients with coronary heart disease can exercise without detectable efflux of CPK or LDH Occasionally, LDH will increase with severe exercise, but in man[20 28] and in rats,[29] this increase in LDH, probably from peripheral tissues, can be obviated by proper prior exercise conditioning Similarly, other investigators[30-32] have reported no rise in either CPK or SGOT activity following a brief period of exercise of varying severity

Exercise and cardiac hypertrophy in young vs old rats It is generally accepted that the heart will increase its ventricular mass in response to exercise or work However, the crucial difference rests in whether the hypertrophy is physiologic or pathologic[33 35] In physiologic hypertrophy muscle fibers increase in size only whereas under conditions which foster pathologic hypertrophy, e g, hypertension the fibers multiply in numbers as well as increase in size which gives rise to impeded diffusion, decreased oxygenation, accumulation of metabolites and ischemia The physiologically hypertrophied rat heart is capable of greater work performance than the normal heart[33] The fact that the old rats responded most positively to swimming exercise may also reside in the diverse manner in which they respond to stress Swimming is stressful to rats and it will cause over stimulation of the parasympathetic nervous system It is possible that the older rats were able to effect more efficient reduction of their heart rate because of a more optimum vagal tone induced by swimming and were thus less susceptible to the tachycardia stimulating effects of isoproterenol. It is also well known that the adrenal corticomedullary response is different in young vs old animals and humans In this connection, we have found that breeder rats which have definitely altered corticomedullary function as well as arteriosclerosis, paradoxically, will withstand isoproterenol induced myocardial infarction in a superior fashion than virgin animals which are in hormonal balance and which have 'healthy arteries[1 5 7] Further, although female rats become much more prostrate than males during acute myocardial ischemia, they survive in greater numbers and effect much more complete repair of their cardiac necrotic sites than males.[1] Again, differences due to hormonal conditioning ' as well as aging must be operative

There is conflicting evidence concerning the effect of exercise on cardiac weight or hypertrophy in rats. We found an increase in the absolute weight of the heart as well as in the heart weight/body weight ratio after exercise in both our young and old rats Ostman, Sjostrand, and Swedin[36] also found that swimming resulted in significant increases in the heart weight of rats. However, Leon and Bloor[24] claim that although exercise will cause cardiac hypertrophy in young rats in contrast to our findings, exercise will cause a decline in the heart size of old rats Further Lee, Karpeles and Downing[37] have shown that the hearts of old male rats are characteristically greatly hypertrophied and have significantly enlarged ventricular chambers Poupa[38] suggests that in the young cardiac subject hypertrophy is secondary to fiber hyperplasia whereas it is secondary to cellular hypertrophy in older animals The above age related factors would account for the poor response of the nonexercised old male rats to the isoproterenol induced myocardial infarction, i e greater cardiac anoxic distress, the delayed onset of serum enzyme changes the appearance of abnormal ECG tracings, as well as inferior survival numerically compared to the younger rats As Froelicher[39] has pointed out if these age dependent responses of the rat heart have any applicability to man then it would imply that exercise programs should begin in childhood because

Case reports

Electrocardiographic and clinical observations of a recurrent tachyarrhythmia arising from a pacemaker within the distribution of the anterior fascicle

James P Goolsby Jr M D *
Philip B Oliva M D **
Denver Colo

Emphasis has recently been placed on predicting the origin of ventricular ectopic beats from the QRS configuration of the scalar electrocardiogram (ECG)[1] His bundle electrograms (HBE) have suggested that ventricular ectopic beats may originate within one of the fascicles of the left bundle branch above the Purkinje tissue[2-4] Cohen and colleagues[5] have reported a case of ventricular tachycardia which appeared to originate within the posterior fascicle of the left bundle The current report presents a patient with a two year history of a recurrent tachyarrhythmia which had previously been thought to be supraventricular in origin The His bundle recording when considered in conjunction with the scalar tracing suggests that the patient has had recurrent anterior fascicular tachycardia This entity has not been previously described to our knowledge

Case report

Patient J F a 50 year old man had a long history of hypertension In 1966 the diagnosis of coarctation of the aorta was made at another institution The patient refused surgery at that time In May 1970 he was admitted to the Denver General Hospital with an acute inferior myocardial infarction confirmed by ECG (Fig 1*A*) and enzymes His course was complicated by numerous arrhythmias including atrial flutter and atrial fibrillation with a rapid ventricular response However on two occasions he developed the rhythm demonstrated in Fig 1*B* This is the arrhythmia which is the subject of this report.

His course over the ensuing two and a half years has been one of frequent hospitalizations and outpatient visits for the tachyarrhythmia shown in Fig 1*B*. Often he would revert to a sinus rhythm spontaneously In no instance was he converted with vagal maneuvers pressors or other drugs including lidocaine procaine amide quinidine digitalis diphenylhydantoin, and propranolol He could, however be easily converted electrically with an energy at 25 to 50 watt seconds Maintenance therapy including various combinations of digitalis procaine amide diphenylhydantoin and propranolol seemed to have little effect on the frequency of his arrhythmias The arrhythmia continued to recur one or two times weekly He was aware of the rapid heart beating but usually had no symptoms referable to the tachycardia The blood pressure decreased slightly during an attack. The arrhythmia often ceased spontaneously after 15 to 30 minutes If it persisted for a longer period he would come to the emergency room or clinic for treatment

In August 1972 he underwent resection of the coarctation and insertion of a short Dacron aortic graft His postoperative course was complicated by two episodes of the same tachyarrhythmia He was cardioverted on these two occasions He was discharged on 0 25 mg. of digoxin per day and 750 mg of procaine amide every four hours

He was seen in the clinic on Sept 22 1972 on a routine visit He was asymptomatic The blood pressure was 110/80 mm. Hg The heart rate was 150 per minute and regular Irregular cannon waves were clearly evident in the neck veins On auscultation the first heart sound was of variable intensity The ECG from this clinic visit has been lost but it was similar to that shown in Fig 1*B* The patient was taken to the cardiac catheterization laboratory where a His bundle recording was done using a No 5 bipolar pacing catheter with electrodes 10 mm apart inserted through the right femoral vein.

After the HBE had been recorded the pacing catheter was left across the tricuspid valve and with the electrodes near the His bundle paced stimuli were delivered at a rate of 330 per minute The patient converted to a sinus rhythm though

From the Departments of Medicine Division of Cardiology of Denver General Hospital and the University of Colorado Medical Center Denver Colo

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Reprint requests to Philip B Oliva, M D Cardiology Division, Denver General Hospital, 790 Cherokee St., Denver Colo. 80204

*Fellow in Cardiology

**Assistant Professor of Medicine University of Colorado School of Medicine Chief Cardiology Division, Denver General Hospital.

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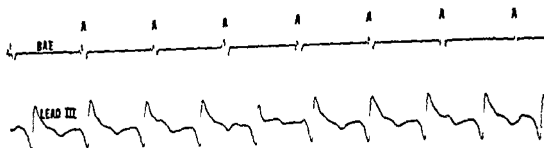


Fig 2A Bipolar atrial electrogram and surface ECG demonstrating A V dissociation with an atrial rate of 117 per minute and a ventricular rate of 150 per minute

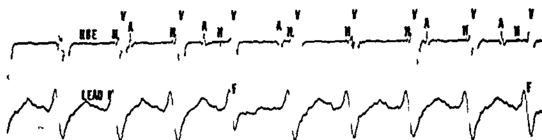


Fig 2B His bundle electrogram and simultaneous surface Lead I demonstrating retrograde depolarization of the His bundle about 55 msec following the onset of ventricular depolarization on the surface lead. The His potential is distinct from the local ventricular depolarization The beats labeled *F* represent fusion beats In this instance the His bundle is depolarized in an antegrade fashion by the preceding atrial impulse

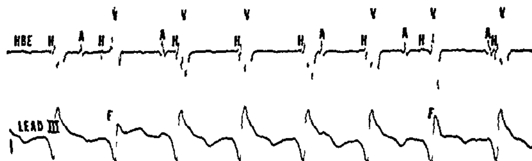


Fig 2C His bundle electrogram and simultaneous surface Lead III Again two fusion beats are recorded. They are preceded by a short H V interval

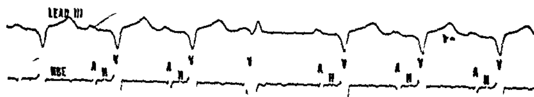


Fig 2D His bundle electrogram and simultaneous Lead III following conversion to normal sinus rhythm The A H interval is 95 msec and the H V interval 58 msec The QRS complexes no longer display the RBBB posterior fascicular block pattern. One premature ventricular contraction is recorded.

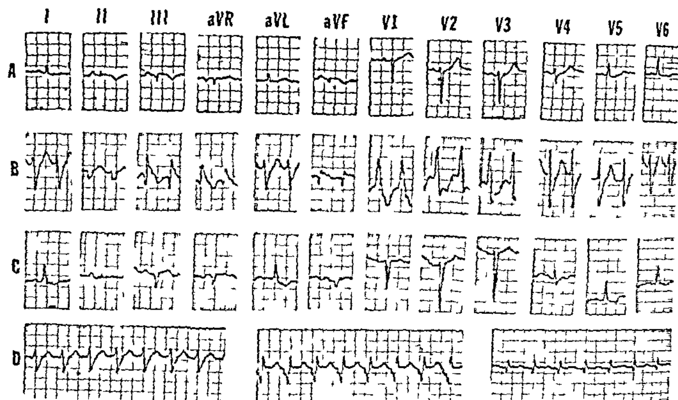


Fig 1 *A* ECG on May 6 1970 demonstrating an acute inferior myocardial infarction *B* ECG on Aug 30 1972 demonstrating the tachyarrhythmia with a RBBB posterior fascicular block configuration The ventricular rate here is slightly less than the ventricular rate when the His bundle recording was done *C* ECG on Sept 12 1972 following conversion to normal sinus rhythm The RBBB left posterior fascicular block configuration of the QRS complexes is not present *D* Rhythm strips of Leads I III and aV_F during a separate episode of the tachycardia to demonstrate the sustained nature

he had frequent premature ventricular contractions as shown in Fig *2D* Following conversion the A H interval was 95 msec and the H V interval 58 msec Fig *1C* shows a standard ECG following conversion to normal sinus rhythm

Results of the intra atrial and the His bundle electrograms Fig *2A* shows the simultaneous intra atrial electrogram and surface ECG This recording shows A V dissociation with a ventricular rate of 150 per minute and an atrial rate of 117 per minute Figs *2B* and *2C* show the His bundle recordings Again A V dissociation is clearly present Note that the majority of complexes show the His potential to follow the onset of ventricular depolarization by 55 msec indicating retrograde conduction to the His tissue Since the scalar tracing shows right bundle branch block (RBBB) and suggests left posterior fascicular block we think that the pacemaker focus is within the anterior fascicle of the left bundle branch or within the Purkinje system of the anterior fascicle

Note in Figs *2B* and *2C* that in an occasional complex labeled *F* the His tissue appears to be depolarized in an antegrade fashion from an atrial impulse The His potential occurs five to 25 msec before the onset of ventricular depolarization In the simultaneous surface ECG the corresponding QRS complexes assume a somewhat different configuration and therefore probably represent fusion beats The interval from the onset of atrial depolarization to the antegrade His potential (A H interval) is 120 to 140 msec This is approximately 40 msec longer than the A H interval following conversion to normal sinus rhythm (Fig *2D*) The longer A H interval during the tachyarrhythmia may be related to the faster atrial rate or to concealed retrograde conduction into the A V node Concealed retrograde conduction is the more likely explanation because the atrial rate decreased by only a few beats following conversion to sinus rhythm and the lengthening of the A H interval during the tachycardia was variable despite a constant atrial rate

It should be said that there may be some doubt about the validity of His potentials recorded on the HBE We believe these are His potentials for several reasons From past experience we have not recorded right bundle potentials as prominent as the deflections labeled "H" in Figs *2B* and *2C* Moreover no right bundle potentials were recorded during sinus rhythm Reversed polarity is not an essential feature of a retrograde His potential [6,8] The polarity of a recorded potential depends on the positional relationship of the conduction pathway to the bipolar electrodes If bipolar electrodes straddle the conduction pathway antegrade and retrograde impulses cannot be readily distinguished.[8] The manner in which the deflection labeled H moves earlier to precede ventricular depolarization in the presence of fusion beats would suggest that it is a His potential

Discussion

The recurrent tachyarrhythmia in this patient had been previously thought to be supraventricular with aberrant ventricular conduction Indeed the patient tolerated the rhythm well with minimal symptoms It remained for the HBE to

may occur through the bundle branches or within infarcted or fibrotic ventricular tissue They thought it possible that myocardial infarction could result in unidirectional block of one bundle branch with resultant single or sustained ventricular beats occurring through a re entry circuit involving the bundle branches Han[14] has shown experimentally that the right bundle branch may conduct an impulse retrogradely to the His bundle and then back to the ventricle through the left bundle branch Theoretically a pattern of RBBB and posterior fascicular block could result from a re entry circuit produced by antegrade conduction through the anterior fascicle and then retrograde conduction through either the right bundle branch or posterior fascicle back to the anterior fascicle The resultant rhythm probably could not be properly termed anterior fascicular since the origin of the rhythm could be any point along the re entry circuit. Of course if re entry were the mechanism of the arrhythmia in this patient the re entry pathway could involve local Purkinje tissue or ventricular myocardium adjacent to the anterior fascicle It cannot be said with any certainty that the rhythm in our patient was re entrant. However conversion to sinus rhythm by pacing the conduction system in the region of the His bundle suggests the possibility of re entry similar to the conversion of ventricular tachycardia by pacing the endocardium of the right ventricle[15]

The temporal relationship of the onset of this patient s rhythm disturbance with his inferior infarction cannot be denied However anatomically one might not expect an anterior fascicular rhythm to result from an inferior infarction Massumi and associates[4] in a recent abstract discuss fascicular beats in the setting of myocardial infarction The fascicular beats tended to originate in the fascicle of the left bundle nearest the infarct Of course our patient could have electrocardiographically silent disease involving or near the anterior fascicle

The frequency of fascicular tachycardias is not known but they are probably not very common Massumi and associates[4] reported that of 33 patients with fascicular ectopic beats after myocardial infarction none developed fascicular tachycardia The natural history of fascicular rhythms remains to be elucidated. Our patient has certainly had a benign course During the arrhythmia his blood pressure is minimally affected, he displays few or no symptoms, and he has never had a transient episode of ventricular fibrillation to our knowledge

The best approach to therapy is also not clear Of note is that our patient was refractory to drug management but converted easily with cardioversion or pacing from the region of the His bundle Termination of a symptomatic recurrent supraventricular tachycardia due to a re entry mechanism by converting a demand ventricular pacemaker to a fixed rate pacemaker has been recently described by Kitchen and Goldreyer[16] It is conceivable that this mode of therapy might be effective in the current case but it has not been considered because the arrhythmias are of so little symptomatic consequence to him

Summary

This report describes a patient with a recurrent tachyarrhythmia refractory to all therapy except cardioversion An intra atrial electrogram demonstrates the presence of A V dissociation The His bundle electrogram demonstrates that the His potential follows the onset of ventricular depolarization in most instances indicating retrograde depolarization of the His bundle Since the QRS complexes during the tachyarrhythmia resemble right bundle branch block with left posterior fascicular block it appears that the rhythm originates within the distribution of the anterior fascicle of the left bundle

Clinical features of the arrhythmia include (1) frequent spontaneous conversion to normal sinus rhythm within 15 to 30 minutes (2) failure of carotid sinus massage digitalis procaine amide propranolol or lidocaine to convert longer attacks (3) consistent termination by cardioversion utilizing 25 to 50 watt seconds, (4) no symptoms referable to the tachyarrhythmia other than palpitations (5) minimal reduction of blood pressure and (6) no known instance of progression to ventricular fibrillation

We would like to thank Virginia Kanyer for her assistance in the preparation of this manuscript and Dr Rashid A Massumi for his review of the His bundle recordings

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clearly show that the rhythm was ventricular in origin

Rosenbaum[1] has emphasized that the form of ventricular extrasystoles may predict their origin Ventricular extrasystoles originating within the Purkinje network of the anterior fascicle of the left bundle will show a pattern of complete RBBB and left posterior fascicular block Rosenbaum also postulates that an impulse arising high within the anterior fascicle of the left bundle branch will inscribe a relatively narrow QRS complex with incomplete RBBB and some degree of left posterior fascicular block The impulse will be propagated in a delayed antegrade fashion down the right bundle branch and the posterior fascicle It seems reasonable that impulses originating further down the anterior fascicle will have greater degrees of RBBB and left posterior fascicular block

Our patient had complete RBBB and left posterior fascicular block during the recurrent arrhythmia It is difficult to be certain whether the rhythm originated in the Purkinje tissue of the anterior fascicle or from the anterior fascicle proximal to the Purkinje tissue The distinctness of the retrograde His potential from the local ventricular depolarization suggests that the origin is within the anterior fascicle Usually with ventricular tachycardia arising more distally the retrograde His potential is buried within the local ventricular depolarization [9,10] Gallagher and colleagues[11] found that during accelerated ventricular rhythms the retrograde His potentials were buried within the ventricular depolarization Occasionally antegrade His deflections were seen during ventricular fusion or capture beats They thought this pattern of His bundle depolarization suggested the origin of the ventricular pacemaker to be somewhere in the distal His Purkinje tissue Damato and associates[8] produced ventricular tachycardia in dogs with digitalis and recorded His left bundle and right bundle electrical activity Two thirds of the dogs developed ventricular tachycardia which appeared to originate within the left bundle In these dogs left bundle His, and right bundle potentials were recorded before or during the initial portions of the QRS complex and were distinct from the local ventricular electrogram One third of the dogs appeared to have the origin of the ventricular tachycardia within the Purkinje network In these dogs His and bundle branch potentials were recorded within the local ventricular electrogram and often could not be distinguished clearly

Yet the long retrograde conduction time of 55 msec from the onset of ventricular depolarization to the His potential is more consistent with a focus in the Purkinje system Electrical stimulation of the right ventricular apical endocardium at a heart rate of 100 per minute resulted in retrograde depolarization of the His bundle at an interval of 45 to 50 msec. following the pacing spike [2,3] With shorter cycle lengths the retrograde conduction time to the His bundle progressively increased. Most isolated fascicular beats display a His potential just before or during the early phase of ventricular depolarization [14] In addition, in the two published examples of sustained posterior fascicular rhythm the His potential preceded ventricular depolarization by a few milliseconds [25] However in these two cases the QRS duration during the arrhythmia was 110 and 100 msec respectively The ventricular complexes displayed an incomplete RBBB configuration with anterior fascicular block It was postulated that the pacemaker arose in the proximal posterior fascicle and was then quickly conducted retrogradely to the His bundle and then traversed the right bundle branch in an antegrade fashion In the current case the QRS duration was 160 msec In addition the ventricular complexes showed a complete RBBB pattern Therefore the V H interval of 55 msec may be explained by assuming that the pacemaker arose in the distal portion of the anterior fascicle or that there was delayed retrograde conduction of the impulse from a more proximal focus

The question of whether fascicular rhythms are automatic or re entrant remains unanswered. Recently, a mechanism for re entry within the Purkinje network has been demonstrated in canine ventricular tissue [12] It seems reasonable that many cases of ventricular tachycardia may involve re entry mechanisms Wellens and colleagues[13] studied five patients with recurrent ventricular tachycardia The ventricular tachycardia in these patients probably involved a re entry mechanism because the tachycardia could be initiated by a single right ventricular premature beat (stimulus delivered via a pacing catheter) or the tachycardia could be terminated by a single right ventricular beat or two right ventricular beats delivered in close succession In addition to the Purkinje network Wellens and associates[13] theorized that re entry

Familial congenital valvular pulmonic stenosis

William E McCarron, M D
Joseph K Perloff M D
Washington D C

Isolated valvular pulmonic stenosis is a relatively common congenital cardiac defect occurring with equal frequency in males and females *Familial* recurrence is a feature of stenosis of the pulmonary artery and its branches[1] and of myxomatous dysplasia of the pulmonary valve[2] but *not* of the classic valvular pulmonic stenosis herein described. This report represents the only confirmed parent child pair with the latter defect.

Case report

Father The father presented as an acyanotic 39 year old Caucasian man with a known heart murmur from age eight years Growth and development were normal Mild breathlessness followed heavy exertion, and frequent epistaxes[1] were described in childhood but the significance of these symptoms was debatable The patient s father was said to have the murmur of pulmonic stenosis but was never investigated. The daughter is described below

Physical examination revealed a man 6 ft 3 in tall and weighing 225 pounds but with otherwise unimpressive physical appearance Blood pressure arterial pulses, and jugular venous pulse were normal. There was a gentle right ventricular impulse but no thrill. A typical pulmonic ejection sound introduced a Grade 3/6 midsystolic murmur that ended just before the first component of a second heart sound that was split in expiration by 50 msec (Fig 1) The electrocardiogram showed a QRS terminal force directed to the right superior and anterior together with an upright T wave *in the right* precordium indicating mild right ventricular hypertrophy The chest x ray (Fig 2 *lower left*) showed normal pulmonary vascularity post-stenotic dilatation of the pulmonary trunk with relative prominence of both left and right branches

From the Department of Medicine Georgetown University School of Medicine Division of Cardiology Georgetown University Hospital, Washington D C

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Reprint requests to Joseph K Perloff M D Section of Cardiology University of Pennsylvania School of Medicine Hospital of the University of Pennsylvania 3400 Spruce St., Philadelphia Pa 19104

Present address. Chief Section of Cardiology University of Pennsylvania School of Medicine Hospital of the University of Pennsylvania, Philadelphia, Pa

Daughter The daughter presented as an acyanotic 14 year old girl with a heart murmur from birth. Growth and development were normal She was asymptomatic except for shortness of breath with moderate exertion and frequent epistaxes in childhood[1]

Physical examination revealed a girl 5 ft 10 in tall weighing 150 pounds Blood pressure and arterial pulses were normal There was a relatively prominent A wave in the jugular venous pulse Examination of the heart detected a systolic thrill at the left base a palpable pulmonic ejection sound at that site and a moderate impulse over the right ventricle The first heart sound was followed by a typical pulmonic ejection sound that introduced a Grade 4/6 mid systolic murmur going just beyond aortic valve closure (Fig 1) Expiratory splitting of the second heart sound was ap

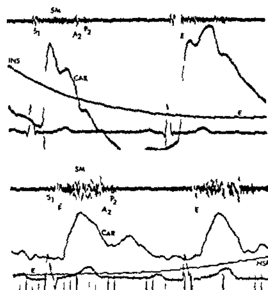


Fig 1 *Upper* Phonocardiogram from father (second left intercostal space) showing a *pulmonic ejection* sound *(E)* that dramatically decreases with inspiration The systolic murmur *(SM)* ends just before A_2 Pulmonary closure (P_2) is delayed by approximately 50 msec *Lower* Phonocardiogram from daughter (second left intercostal space) showing a prominent pulmonic ejection sound, a pulmonic stenotic murmur that extends just beyond A_2 and a soft P_2 delayed by approximately 80 msec

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Table I Catheterization data

	Pressures (mm. Hg)					
	Father			*Daughter*		
Right atrium	A	4		A	12	
	V	1		V	9	
	Mean	1		Mean	8	
Right ventricle	Systolic	40	70	Systolic	85	105
	Diastolic	6	12	Diastolic	11	
Pulmonary artery	Systolic	18		Systolic	18	
	Diastolic	8		Diastolic	10	
Cardiac output	5 5 L/min.	(Dye dilution)		5 9 L/min	(Dye dilution)	
Cardiac index	2 41 /min./M 2			3 2 L/min./M 2		

Immediately post angiogram

main line index ATD angle A B ridge count and axial t distance for the palms There were no uniquely common dermatoglyphic features although the daughter had a rare configuration of whorls in the interdigital areas of both palms

The mother of the family and the two remaining siblings (one sister and one brother) were seen clinically A careful history physical examination electrocardiogram and cardiac x ray series in each disclosed no suspicion of heart disease

Discussion

The frequency of congenital heart disease in parents of affected children is low [3] There is the prospect however that increasing numbers of operated congenital cardiac patients will reach childbearing age and will produce a higher incidence of offspring with congenital defects of the heart or circulation [4] Currently the incidence of parent child pairs with identical congenital cardiac defects is vanishingly small but has been reported in aortic stenosis, atrial septal defect and ventricular septal defect [5] Our father and daughter with classic valvular pulmonic stenosis represent the first confirmed parent child pair with this form of identical congenital cardiac disease

Summary

This is an account of the only known parent child pair with classic isolated congenital valvular pulmonic stenosis Both patients had phonocardiograms electrocardiograms vectorcardiograms chest x rays cardiac catheterization and angiocardiography In addition genetic information was sought from fingerprints palm prints hair and iris color facial characteristics colorblindness tests blood typing and antigens and degree of kinship existing in the family tree

We wish to thank Dr Milton Alter Chief Neurology Service Veterans Administration Hospital Minneapolis for his meticulous dermatoglyphic analysis We also wish to thank Dr Gerald Sandler Georgetown University Hospital Washington D C for providing us with blood type and blood antigen information

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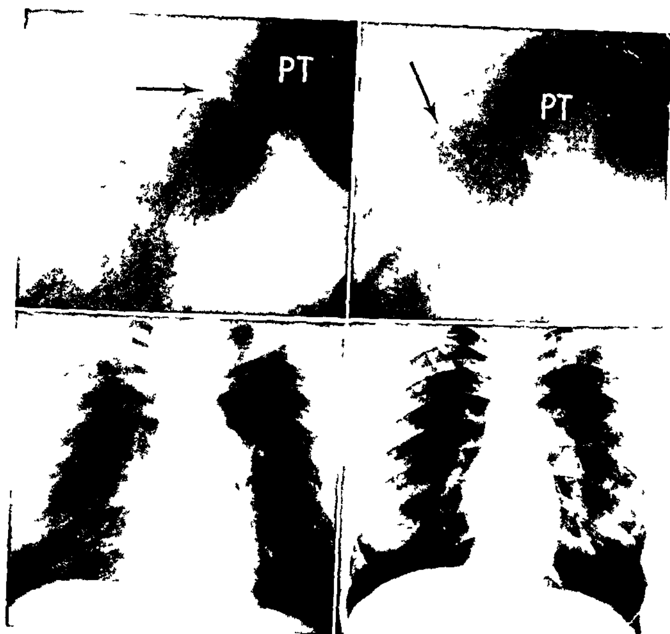


Fig 2 *Upper* Angiocardiograms of father and daughter respectively showing the stenotic pulmonary valves *(arrows)* and poststenotic dilatation of the pulmonary trunks *(PT)* *Lower* Chest x rays of father *(left)* showing dilatation of the pulmonary trunk with relative prominence of both main branches and daughter *(right)* showing dilatation of the pulmonary trunk disproportionate dilation of the left branch and a moderately prominent right atrial convexity

proximately 80 msec and pulmonary closure was comparatively soft (Fig 1) The electrocardiogram showed slightly peaked P waves of right atrial hypertrophy right axis deviation with a 15 mm monophasic R wave in V_{3R} and V_1 together with persistent upright T waves in the right precordium indicating right ventricular hypertrophy with estimated right ventricular pressure near systemic levels Chest x ray (Fig 2 *lower right*) showed normal pulmonary vascularity post stenotic dilatation of the pulmonary trunk and left branch and slightly prominent right atrial convexity

Cardiac catheterization information (father and daughter) is shown in Table I The father had a pulmonary valve gradient of 22 mm Hg rising to 52 mm Hg after right ventricular angiography The daughter had a 67 mm Hg gradient rising to 87 mm Hg after right ventricular angiography

Vectorcardiograms in each patient revealed clockwise loops in the frontal plane with anterior and clockwise loops in the horizontal plane The maximum anterior to posterior displacement ratios of the QRS loop in the horizontal plane exceeded one in both patients

Fig 2 *(upper)* shows angiocardiograms of the outflow tract pulmonary valve *(arrow)* and pulmonary trunk *(PT)* in father and daughter The features are typical of classic valvular pulmonic stenosis with post stenotic dilatation

Blood antigens were nearly identical in father and daughter including the ABO Rh MNS Kell Duffy Kidd P and Lewis systems Phenotypically the father and daughter resembled each other in tall stature similar hair and iris colors and similar facies The kinship in the available family tree was not consanguineous

Dermatoglyphic study included pattern and ridge counts for the fingers in addition to interdigital main line formula

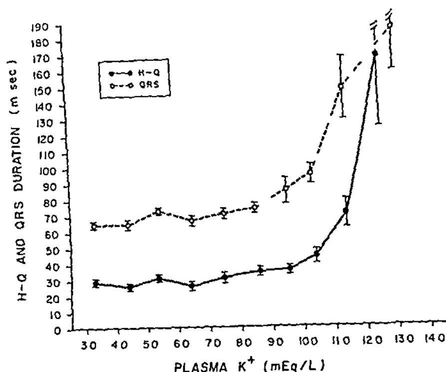


Fig 1 H Q and QRS duration as functions of increasing plasma K in 10 dogs At concentrations above 8 to 9 mEq per liter both are prolonged As K rises above 10 mEq per liter small increments of plasma K^+ induce large conduction changes Means and standard errors are indicated

carefully monitored at all plasma concentrations. Zwaardemaker[18] and Libbrecht[19] described cardiac arrest occuring even during K^+ replacement at hypokalemic levels and a clinical report echoed the need for caution[20] The electrical mechanism of arrest[21] under these circumstances appears to differ from that occurring during hyperkalemia however

Effect of increased K^+ upon action potentials

Increasing extracellular K regularly lowers (makes less negative) resting membrane potential and shortens the duration of the action potential in all cardiac tissues[11-2] The former effect is due to a decreased transmembrane gradient of K whereas the latter has been attributed to increased membrane permeability to K A decline in upstroke velocity (phase 0) accompanies the reduction in resting potential thus reducing the velocity of conduction between adjacent cells The fall in resting potential results naturally from reduction of the usually large intracellular/extracellular concentration gradient as extracellular K rises, since that potential is created in major part by this gradient across the semipermeable cell membrane An excess of sodium or calcium ion can be shown to limit the depolarization caused by high K^+[23,24] hence the effectiveness of these ions in the treatment of hyperkalemic arrhythmias In Purkinje cells hyperkalemia reduces the slope of diastolic depolarization thus reducing the rate of discharge

Effects on the ECG and cardiac conduction

Action potential shortening causes shortening of QT which may be observed even at modest hyperkalemia (K^+ = 6 to 7 mEq per liter) Some increase in the height of T may occur producing the tented T waves of toxicity often described. However these occur only in a minority at this level[23] but more regularly at K^+ = 8 to 9 mEq per liter Slight shortening of the PR interval is sometimes observed at modest hyper K^+ in vitro[25] and in vivo[8] measurement of conduction velocities through the atrioventricular (A V) system indicate most rapid transmission at these concentrations At levels of K in excess of 8 to 9 mEq per liter conduction becomes progressively impaired As atrial muscle is especially sensitive

Hyperkalemia, cardiac conduction, and the electrocardiogram A review

Philip O Ettinger M D
Timothy J Regan M D
Henry A Oldewurtel
Newark N J

Cardiac arrest due to hyperkalemia was first described by Hering[1] in 1907 Four years later Mathison[2] observed heart block in cats following potassium (K⁺) administration Numerous subsequent reports have indicated that gradually increasing plasma K⁺ induces a biphasic, more or less reproducible electrical sequence of initial increase then profound decrease in impulse formation and conduction in all cardiac tissues In the experimental animal, heart block and asystole is the almost invariable finale to progressive hyperkalemia[3-8] although ventricular tachycardia and fibrillation occur occasionally In hyperkalemic man progression to heart block is unusual a variety of arrhythmias have been reported although, as will be seen, the question of ventricular vs supraventricular origin of these disturbances does not always lend itself to simple resolution[9-11] The purpose of this review is to summarize the electrophysiologic effects of increased K⁺ on the various cardiac tissues, to correlate these electrical changes with changes in the peripheral electrocardiogram (ECG), specialized fiber and intramural electrical recordings and with mechanical events in the heart Perspective may be derived from these observations into the relationships between increased K⁺ conduction delay, asystole and arrhythmias

From the Department of Medicine College of Medicine and Dentistry New Jersey Medical School Newark N J

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Reprint requests to Philip O Ettinger M D New Jersey Medical School 100 Bergen St. Newark N J 07103

Clinical settings

Hyperkalemia in man occurs most frequently in renal failure and may induce serious cardiac rhythm disturbances While this is undoubtedly the most common cause of increased K⁺, it may also be observed in untreated diabetic ketoacidosis and in adrenocortical insufficiency The overly rapid administration of exogenous K⁺-containing electrolyte solutions, stored blood, or medications with high K⁺ content,[12] especially certain penicillins[13] may also induce hyperkalemia Increased K⁺ occurred with a frequency of 12 per cent following cardiac surgery with extracorporeal circulation at one center[14] This complication occurred early in the postoperative period and related to a variety of factors including oliguria, extravascular collections of blood, multiple transfusions, hemolysis, and acidosis Diuresis under these circumstances sometimes induced hypokalemia Although hyperkalemia was occasionally diagnosed from the ECG cardiographic findings suggesting altered K⁺ were relatively frequent after cardiac operations even in patients with normal K⁺ concentrations[14]

Intravenously administered K⁺ salts enjoyed a brief popularity as antiarrhythmics (see below) but their hazards soon relegated them to the status of drugs of last resort Similarly oral K⁺ was suggested as a diagnostic agent to distinguish organic from functional T wave abnormalities in the ECG[15-17] but induced arrhythmias and sudden deaths resulted and dampened enthusiasm for its continued use[16,17]

While we are concerned here with the effects of increased plasma K⁺ (in excess of the normal range of 3 7 to 5 2 mEq per liter) it should be noted that K⁺ administration must be slow and

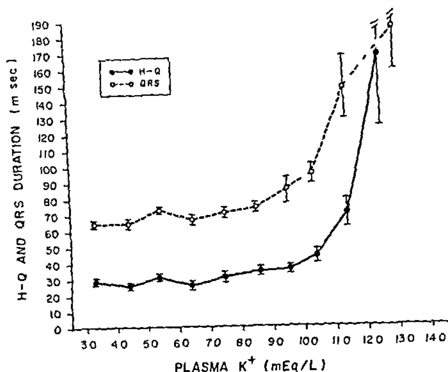


Fig 1 H Q and QRS duration as functions of increasing plasma K^+ in 10 dogs At concentrations above 8 to 9 mEq per liter both are prolonged. As K^+ rises above 10 mEq per liter small increments of plasma K^+ induce large conduction changes Means and standard errors are indicated.

carefully monitored at all plasma concentrations Zwaardemaker[18] and Libbrecht[19] described cardiac arrest occuring even during K^+ replacement at hypokalemic levels and a clinical report echoed the need for caution [20] The electrical mechanism of arrest[21] under these circumstances appears to differ from that occurring during hyperkalemia however

Effect of increased K^+ upon action potentials

Increasing extracellular K regularly lowers (makes less negative) resting membrane potential and shortens the duration of the action potential in all cardiac tissues [11,22] The former effect is due to a decreased transmembrane gradient of K whereas the latter has been attributed to increased membrane permeability to K A decline in upstroke velocity (phase 0) accompanies the reduction in resting potential thus reducing the velocity of conduction between adjacent cells The fall in resting potential results naturally from reduction of the usually large intracellular/extracellular concentration gradient as extracellular K rises since that potential is created in major part by this gradient across the semipermeable cell membrane An excess of sodium or calcium ion can be shown to limit the depolarization caused by high K^+[23,24] hence the effectiveness of these ions in the treatment of hyperkalemic arrhythmias In Purkinje cells hyperkalemia reduces the slope of diastolic depolarization thus reducing the rate of discharge

Effects on the ECG and cardiac conduction

Action potential shortening causes shortening of QT which may be observed even at modest hyperkalemia ($K^+ = 6$ to 7 mEq per liter) Some increase in the height of T may occur producing the tented T waves of toxicity often described. However these occur only in a minority at this level[23] but more regularly at $K^+ = 8$ to 9 mEq per liter Slight shortening of the PR interval is sometimes observed at modest hyper K^+ in vitro[25] and in vivo[8] measurement of conduction velocities through the atrioventricular (A V) system indicate most rapid transmission at these concentrations At levels of K^+ in excess of 8 to 9 mEq per liter conduction becomes progressively impaired. As atrial muscle is especially sensitive

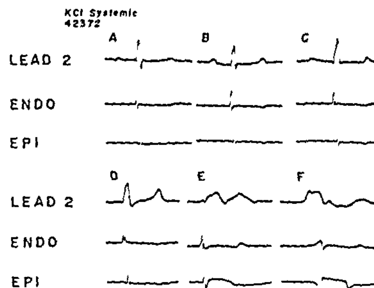


Fig 2 ECG Lead II with simultaneous endocardial (*endo*) and epicardial (*epi*) bipolar electrograms during progressive hyperkalemia *A* to *F* indicate progressive stages during infusion While QRS widens and conduction time between endocardial and epicardial activation increases the height and measured QT of the electrograms decreases As P waves disappeared after C *D* to *F* show only the QRS T When QRS is very wide the transmural activation sequence changes suggesting that activation of the ventricle no longer occurs from inner to outer wall at the electrode site In *E* *endo* and *epi* potentials are almost simultaneous while in *F* *epi* actually precedes *endo* Activation may progress laterally through the wall at this late phase but the actual direction cannot be determined from these measurements Paper speed 200 mm per second

to depolarization by K^+ while the specialized fibers of the S A and A V nodes are less affected,[26 27] the P wave of the ECG becomes progressively lower in amplitude and the PR lengthens Ultimately P may disappear from the peripheral ECG although sinoventricular conduction may continue from S A node to the ventricles via specialized atrial fiber pathways and can be demonstrated by intracardiac recordings [3]

Investigations of cardiac conduction by electrode catheter and intramural electrode techniques in our laboratory and others have clarified some of the alterations that occur Briefly electrode catheters were placed in anesthetized dogs (1) at the aortic valve and (2) anteriorly in the left ventricular chamber to record His bundle and left anterior divisional electrograms, respectively by techniques previously described in the dog[28,29] and in man [30 31] Bipolar electrograms from these sites were recorded simultaneously with the peripheral ECG In other dogs bipolar stainless steel wire electrodes[3 33] were implanted during thoracotomy in the endocardium and epicardium of the free wall of the left ventricle so that the two bipolar pairs lay along a perpendicular line traversing the wall at that point In this way conduction times could be measured from P wave to His, from His to left bundle from His to onset of QRS (H Q or H V) and from endocardium to epicardium In addition the relative degree of endocardial and epicardial action potential voltage reduction (height of electrogram spike) and shortening (QT_c of electrogram) could be ascertained during hyperkalemia which was induced by infusing isotonic KCl solution into a peripheral vein at 1 7 to 3 4 mEq per minute

Correlation of recorded H Q and QRS duration with increasing plasma K^+ levels is indicated in Fig 1 Both are seen to increase rapidly at $K^+ > 9$ to 10 mEq per liter Widening of QRS was accompanied by lengthening of QT but intramural electrogram QT_c shortened (Fig 2) indicating that the apparent QT lengthening in the peripheral ECG was due entirely to increasingly greater delay in the activation of different regions of the ventricles The degree of endocardial and epicardial electrogram change was parallel to be expected during a systemic infusion likely to cause homogeneous K^+ increases in all portions of myocardium Uniform K^+ increase across the wall (and in different regions of the ventricle) was demonstrated in these animals after asystole had occurred by direct analysis of ventricular muscle (Fig 3)

Heart rate slowed somewhat in many animals at $K^+ > 10$ mEq per liter although this was variable As H Q increased the His complex itself became wider, slurred and of reduced amplitude

QRS widened initially of similar configuration to control but later became distorted to indicate variations in activation sequence The pattern of QRS widening is not specific for hyperkalemia although spontaneously occurring conduction disturbances associated with QRS prolongation are not accompanied by QT shortening Surawicz and associates[5] have indicated and our studies confirm that even after marked QRS and apparent QT prolongation due to increased K^+ the [QT QRS] interval always remains shorter than normal As conduction prolongation progresses with hyperkalemia the QRS may superficially resemble right or left bundle branch block but

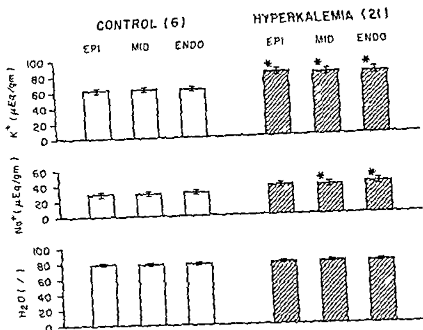


Fig 3 Potassium sodium, and water content of the left ventricle at the time of asystole caused by KCl infusion Potassium is uniformly increased across the wall while tissue water is unchanged. Sodium is also uniformly increased, although the mechanism for increment of this ion is unknown *Epi, mid* and *endo* refer to outer middle and inner thirds of a transmural segment of left ventricular free wall Asterisks indicate significant change from normal content.

usually appears nonspecifically widened [8,11,23] Occasionally patterns resembling infarction (Q waves) are seen[34] and ST segment elevation has been reported [35] While not routinely distinguishable by surface ECG the QRS widening due to K^+ affects all portions of the loop rather than only middle or terminal segments as occurs in spontaneously occurring bundle branch block

In the hyperkalemic dog R R intervals usually became irregular at $K^+ \sim 10$ mEq per liter As QRS was widened and now unrelated to P wave activity (if P was still visible) a diagnosis of ventricular arrhythmia might have been made if only the surface ECG were available for analysis His bundle studies, however almost always showed His bundle activity preceding each QRS (Fig 4) Sometimes typical Wenckebach periodicity of QRS was observed, indicating progressive A V nodal block Other investigators have also shown that failure of A V conduction occurs commonly at this stage of hyperkalemia [7] We did not observe sinoventricular conduction to continue at $K > 10$ mEq per liter Even though atrial potentials disappeared from the standard ECG intra atrial electrodes continued to record them at their control rate At this stage accelerated junctional pacemakers appeared most likely to have been the origin of impulses conducted to the ventricles as excess K^+ in man slows the primary pacemaker but may accelerate subsidiary centers [36]

Further increases in K^+ ultimately resulted in asystole in the large majority of experimental studies due to block in the distal ventricular Purkinje system In our experience asystole was often associated with continued passage of conduction impulses down the Purkinje network (Fig 4) While the electrode catheter technique cannot further localize the conduction block conduction appeared to stop at the Purkinje fiber-muscle junction in an in vitro preparation [37] although block at the electrical gate in the distal Purkinje fiber seems theoretically plausible At about the time that asystole occurred, intramural electrodes often indicated change in the sequence of endocardial and epicardial depolarizations (Fig 2) indicating altered intramural activation When the asystolic heart was then removed from the chest rhythmical slow waves of contraction often began spontaneously and rolled across the cardiac surfaces indicating the simultaneous presence of depolarization and repolarization processes in different regions [4] Continued conduction

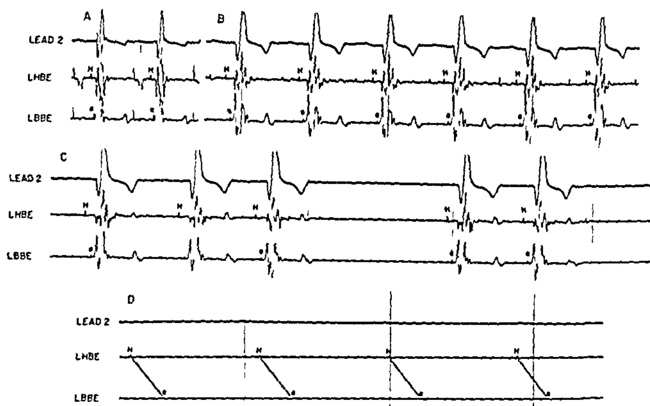


Fig 4 Lead II ECG His bundle electrogram recorded from aortic root *(LHBE)* and left bundle branch electrogram *(LBBE)* recorded from within the left ventricle during progressive hyperkalemia *H* indicates His depolarizations *a* the bundle branch impulses (anterior false tendon recording) *A*, Control Atrial pacing was employed initially to maintain rate constancy *B*, P waves are still visible H Q and H a intervals are increased. QRS is widened but with the same configuration as control *C*, Slightly later H Q and H a are longer P waves are no longer visible although the *LHBE* suggests that atrial activity may still precede the *H* impulses There is a pause between the third and fourth beats which may be due in part to failure of an atrial impulse to pass through to the His recording site Accurate evaluation of the rhythm is often difficult at this phase *D* Asystole Impulses continue to pass from His to bundle branch recording sites but fail to activate the ventricles Paper speed 200 mm per second time lines, 1 per second

fiber depolarizations after asystole indicate the lesser sensitivity of Purkinje tissue to hyperkalemia as compared with ventricular and atrial muscle

Arrhythmias thus induced by K^+ tend to show low or absent P waves with wide QRS complexes if the rate of QRS is rapid then a ventricular tachycardia is usually suggested by morphology All of the animals studies described above, however indicate that the majority of these arrhythmias are probably of junctional or even sinus node origin with QRS widening due to conduction slowing We are not aware of any His studies obtained during so called ventricular tachycardia in hyperkalemic man In a few instances rapid rhythms with wide QRS did occur in our animals, true ventricular tachycardia could not be ruled out with the electrode catheter technique [6] Nevertheless it would appear likely that many (if not most) of the so called ventricular tachycardias observed in hyperkalemic man rather represent accelerated junctional or even sinoventricular rhythms with aberrated QRS It should be emphasized that the rate of administration of K^+ may affect the types of conduction and rhythm disturbances observed [5] Rapid increases in K^+ tend to induce bradycardia and depression of contractile force and may be associated with ventricular fibrillation slow increases lead predominantly to conduction prolongation and asystole

Hemodynamic changes during hyperkalemia

No human studies of ventricular function in hyperkalemia have been reported *In our* dog studies, systemic pressure and left ventricular dp/dt max were unchanged until K^+ exceeded 10 mEq per liter and coronary flow remained unchanged as well (Fig 5) LVEDP increased progressively The parallel reductions in contrac

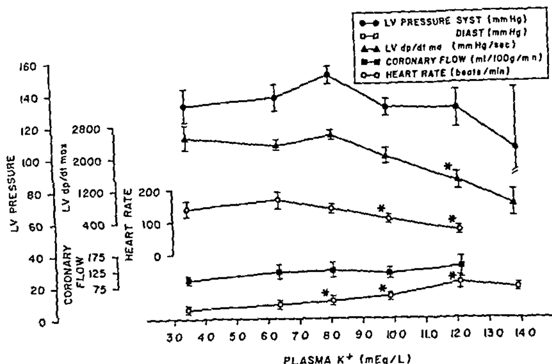


Fig 5 Hemodynamic changes during progressive hyperkalemia Left ventricular systolic pressures and dp/dt max fell only at K+ > 10 mEq per liter Left ventricular end diastolic pressures rose progressively Coronary flow was unchanged, while heart rate fell at K+ > 10 mEq per liter

tility and conduction velocity suggest that contractile changes during greatly increased K+ may result directly from the conduction changes occurring simultaneously While contractility has been reported to decline progressively in the isolated heart during hyperkalemia [38,39] other investigations of the intact animal agreed with our findings [40,41]

Pacing during hyperkalemia

The excitability of the heart to electrical pacing as K rises is probably biphasic Several investigators have shown a transient decrease[42-44] in diastolic threshold at slight hyperkalemia (K ~ 5 to 7 mEq per liter) but other studies failed to confirm this decline [8,45] Restoration of pacing following failure due to subthreshold stimulation has been reported after oral or intravenous administration of K [44,46,47] Since disagreement has been expressed over whether a true increase in excitability is present in this range it was suggested that apparent decreases in the pacing threshold may result from asynchronous changes in resting potential and threshold potential [43] Both resting potential and threshold potential are made less negative by increased K+ but changes in pacing threshold would depend upon which was more affected A transient lowering of threshold could occur during rapid K+ infusion if resting potential rose rapidly while threshold potential rose only sluggishly As pacing threshold determinations are affected by local conduction changes at the stimulus site as well as by threshold, failure or acceleration of local propagation could affect threshold, so that even if excitability of cells remained constant, the slightly enhanced conduction velocity at K+ 5 to 7 mEq per liter might explain a decreased pacing threshold.

Despite controversy about excitability at K+ = 5 to 7 mEq per liter, it is generally agreed that excitability decreases and pacing threshold increases at K > 8 mEq per liter [42-49] However, pacing of the ventricles may still be accomplished even during severe hyperkalemia [50] In our own dog experiments ventricular pacing with maintenance of normal systemic pressure could often be continued long after asystole had occurred due to failure of intrinsic impulse conduction [8] Ventricular pacing is the emergency treatment of

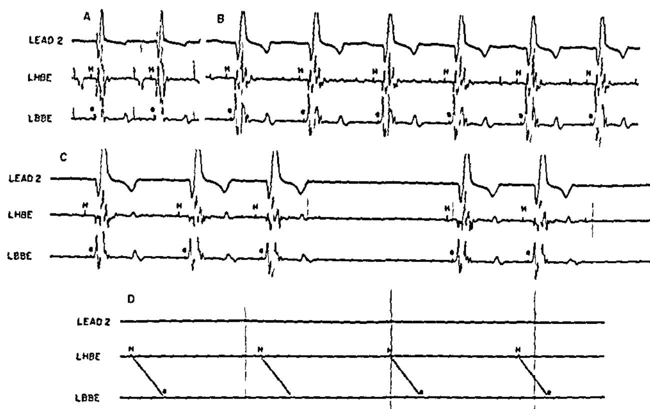


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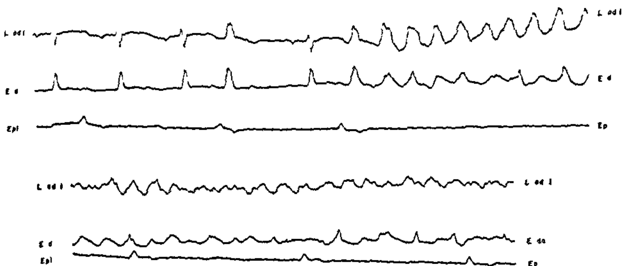


Fig 7 Top Onset of ventricular tachyarrhythmias just after Fig 6 E Severe intramural block is present and when 1 1 conduction occurs the epicardial depolarizations are especially slurred. When the arrhythmia begins the epicardial electrogram is almost flat Bottom Ventricular fibrillation is seen in Lead I ECG and endocardial potentials Epicardium appears not to participate but instead depolarizes slowly Paper speed, 200 mm. per sec ond time lines 1 per se ond. (Reproduced from Ettinger et al., Circ Res 33 621 1973 by permission of the American Heart Association Inc)

cent glucose with 25 to 50 U of regular insulin intravenously should be begun to drive the extra cellular K into intracellular sites Oliguria and acidosis must be corrected with appropriate agents any responsible drugs or biologicals (spironolactone triamterene bank blood potassium chloride or iodide K^+ containing penicillins) should be sought and removed from the therapeutic regimen Dialysis is not usually required in the acute phase of management, although underlying renal disease may subsequently suggest it. All methods to reduce plasma K run the inevitable risk of inducing hypokalemia regular determination of plasma K^+ is required during therapy

Potassium induced cardiac arrhythmias

As will be apparent from the foregoing the primary electrical effects of K on the heart at concentrations > 7 mEq per liter are progressive depressions of excitability and conduction velocity While the effects are transiently opposite at ~ 5 to 7 mEq per liter they are relatively small and of questionable clinical significance If the results of the numerous sy temic K studies in animals may be extrapolated, true ventricular arrhythmias are probably uncommon in hyperkalemic man except as terminal phenomena As K^+ rises slowly sequential changes include A V junctional delay with or without so called sino ventricular conduction followed by acceleration of junctional pacemakers and conduction delays in the ventricular specialized tissue and muscle Heart block may occur rarely Occasionally, rhythms resembling ventricular tachycardia supervene The sometimes bizarre and widened QRS in animal studies is almost invariably produced by conduction from above with aberration Human hyperkalemia usually arises in a milieu of other metabolic problems however and it is possible that true idioventricular rhythms are more commonly induced than in animals In particular hypocalcemia and hyponatremia may aggravate and modify the effects of increased K^+ alone

An interesting contrast between generalized and local conduction slowing is provided by comparing the effects of systemic hyperkalemia and those induced in a localized area of myocardium by intracoronary infusion of K^+.[64-69] Local cardiac hyperkalemia results in ST segment elevation and ventricular arrhythmias The latter have been studied in our laboratory and are probably of re entrant origin[69] During a typical intracoronary K^+ infusion we monitored conduction as before with His and left bundle branch

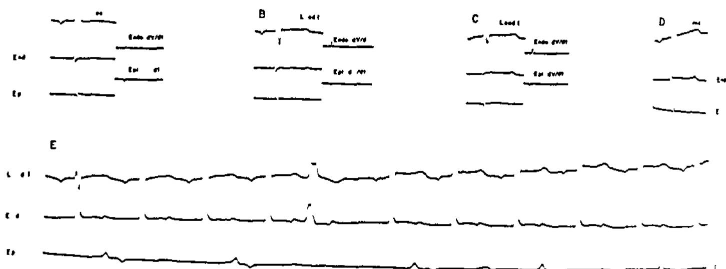


Fig 6 Lead I ECG endocardial *(endo)* and epicardial *(epi)* electrograms from the left anterior descending coronary artery region during regional perfusion with K⁺ *A* Control with dV/dt s *B* to *D* ST segment elevation is present. Electrogram voltages are lower as are dV/dt s *E* Onset of ventricular extrasystoles While Lead I shows no change from before slurring of the electrograms is apparent. Delay from endocardial to epicardial activation is greater than previously with epicardial activation occurring during the T wave of the surface ECG QTc is shorter than control Paper speed 200 mm per second time lines 1 per second (Reproduced from Ettinger et al Circ Res 33 521 1973 by permission of the American Heart Association Inc)

choice in severe bradycardia or asystole caused by hyperkalemia

Potassium as an antiarrhythmic agent

Before the development of more satisfactory antiarrhythmic drugs infusion of potassium salts had been utilized clinically to treat atrial and ventricular tachyarrhythmias [51,60] The effectiveness of this agent may have been due either to transient conduction acceleration at modest K⁺ increase or depression at higher K⁺ as it may be hypothesized that either alteration could terminate a re entrant arrhythmia requiring a conduction pathway of critical duration Alternatively depression of excitability at higher K⁺ would tend to suppress ectopic foci It has been suggested that the automaticity of ectopic pacemakers is depressed by K⁺ earlier than that of the S A node [61] Use of this agent was found to be hazardous as K⁺ induced A V block and arrhythmias were not uncommonly produced [16,17] Additionally it was soon found to potentiate digitalis induced A V block [62] The limitations of its use have been summarized [11,23,63] and the present use of K⁺ in arrhythmias has been in large part limited to treatment of digitalis induced paroxysmal atrial tachycardia with block It is not a specific agent for the treatment of digitalis induced arrhythmias Its hazards may be understood by considerations of the conduction depressing effects of K⁺ (Fig 1) where it is seen that small increases in K⁺ above about 9 to 10 mEq per liter risk major conduction prolongation Operating within this range might be expected to induce serious secondary conduction problems with minimal increments of dose

Treatment

Hyperkalemia requires prompt therapy directed against both the elevated K⁺ ion and the underlying cause Plasma K⁺ in the 5 0 to 7 0 mEq per liter range and associated with sinus rhythm and narrow QRS may respond well to oral or rectal administration of sodium polystyrene sulfonate resin (Kayexalate), 12 to 16 Gm three or four times per day Widened QRS and arrhythmia requires urgent treatment Temporary transvenous pacing of the ventricle is the treatment of choice for asystole bradycardia or A V block Rapid tachyarrhythmias are best treated with prompt intravenous administration of sodium or calcium ion Intravenous administration of sodium bicarbonate 44 to 132 mEq or even saline tends to reverse the ECG abnormalities as does calcium gluconate or chloride 10 ml of 10 per cent solution intravenously As these ions do not themselves lower K⁺ concentration an intravenous infusion of 500 c c of 10 per

bances especially hyponatremia and hypocalcemia A V block is not often observed (? recognized) in man

Ventricular pacing threshold may initially decrease (increased excitability) but profound subsequent increases occur as K^+ rises further In the experimental animal potassium and sodium ion concentrations increase uniformly across the myocardial wall Ventricular pressure and dp/dt max tend to fall only after marked QRS prolongation causes the ventricle to contract asynchronously

While K has been administered as an antiarrhythmic agent its use involves potential hazards especially during the simultaneous use of digitalis It should probably not be used for this purpose except perhaps in digitalis induced paroxysmal atrial tachycardia with block Although slow systemic increase of K^+ induces asystole in animals administration to a region of myocardium produces ventricular ectopic beats and fibrillation The latter effect may be due to re entry and may be mechanistically similar to the arrhythmias of early ischemia

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recording catheters and with bipolar electrodes at endocardial and epicardial levels in the perfused zone ST segments rose progressively in the perfused region despite normal coronary flow, animals progressed rapidly to multifocal VPC s and ventricular fibrillation QRS was locally prolonged within the perfused zone, but His or bundle branch depolarizations were never seen to precede extrasystoles and the sequence of ventricular activation during extrasystoles in this zone was sometimes reversed, suggesting origin of VPC s within the myocardium Of importance (Figs 6 and 7) was the finding that arrhythmia began at the time that conduction from inner to outer wall became sufficiently delayed that re entry from depressed epicardial layers into more normal surrounding tissue became possible The degree of tissue K^+ increment within the perfused zone was never as severe as that observed throughout the myocardium in systemically infused animals These observations indicate that homogenous increment of myocardial K^+ (systemic hyperkalemia) induces uniform conduction delay which is not under ordinary circumstances productive of ventricular extrasystoles whereas hyperkalemia in a region of heart muscle is seriously arrhythmogenic

Harris and associates[70,71] initially suggested the importance of K^+ liberation from ischemic cells in the development of ventricular arrhythmias during experimental myocardial infarction Earlier investigations from this laboratory indicated that K^+ egress from a large ischemic area into the venous effluent preceded ventricular ectopic activity, and that treatment with procaine amide reduced this ionic loss[72] Ischemia increases extracellular and reduces intracellular K^+, thus reducing the intracellular/extracellular ratio Local K^+ infusions probably alter this ratio similarly by increasing extracellular K^+ Regional hyperkalemia also induces regional asymmetry of refractoriness as well as local conduction slowing both of which alterations have been considered to predispose to fibrillation during ischemia Of great interest is the recent demonstration that during ischemia marked epicardial conduction delay may similarly precede the arrhythmic phase[73,74] Thus local K^+, released from injured myocardial cells may be responsible for re entrant ventricular arrhythmias in a manner similar to that observed during local hyperkalemia In experimental preparations of in vitro Purkinje strands and papillary muscle recent investigators utilized high concentrations of K^+ and K^+ with epinephrine to slow conduction severely enough that re entry was demonstrated.[75,76] While these experimental conditions may not exist in Purkinje fibers in vivo it is possible that they do exist in regions of ischemic muscle

A discussion of K^+ induced arrhythmias would be incomplete without a historical reference to the early work of Wiggers[77] In his investigations of ventricular fibrillation he found that fibrillation could be terminated by inducing complete cessation of cardiac activity with K^+ then washing that ion out of the heart return to regular rhythm followed. Technical problems and the invention of the defibrillator made this approach obsolete However, K^+ induced cardioplegia may yet find new therapeutic usefulness to arrest the heart during cardiac surgery[78]

Summary

Increased plasma potassium may occur spontaneously or iatrogenically At modest hyperkalemia ($K^+ \sim 5$ to 7 mEq per liter) a transient and minor acceleration of cardiac conduction can be demonstrated but profound and rapid depression of conduction occurs progressively at $K > 8$ to 9 mEq per liter Examination of the peripheral ECG reveals inconstant peaking of T waves during modest elevation As K^+ rises however PR prolongs and P ultimately disappears QRS widens and R R intervals become irregular Sinoventricular conduction may be observed at this stage Later sequential changes include atrioventricular junctional delay followed by acceleration of junctional pacemakers conduction delays in the His Purkinje system, and delays in ventricular muscle As K^+ rises in animals asystole is the predominant mechanism of cardiac arrest. His bundle and bundle branch recordings indicate that asystole typically arises from block within the distal conducting system The resultant peripheral ECG shows regular or irregular rhythm with widened QRS although the morphology of the QRS may suggest that the arrhythmias are of ventricular origin animal experiments almost invariably identify the rhythms as junctional or sinus In man the effects of K^+ upon the ECG are greatly modified by other electrolyte distur

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the changes in contour due to tricuspid valve closure completely disappeared and only the carotid artifact C wave remained

The X descent and the systolic jugular collapse

The next atrial event is produced by further ventricular contraction Cineangiograms of a ventricle demonstrate that the base of the ventricle (floor of the atrium) *descends* toward the apex with ventricular systole Physiologists have called this the systolic descent of the base meaning the descent of the A V ring Since the atria are firmly attached by their tributary veins to surrounding structures pulling down of the atrial floor results in a decline in atrial pressure This fall in atrial pressure during systole produces a descent in the atrial and jugular pulses Physiologists have called this venous collapse during systole "the systolic collapse of the venous pulse

The other explanations for the systolic jugular descent do not stand up well against criticism. Atrial relaxation has been said to be partly responsible Since this requires that the atrium continues to expand during ventricular systole this explanation should be abandoned except in reference to the left atrium in the presence of mitral stenosis. Some studies have indeed shown that atrial relaxation can occur during ventricular systole and therefore can contribute to the descent after the C wave But this phenomenon has been shown only in the left atrium, and only in the presence of mitral stenosis [31,32] It is known that in mitral stenosis the left atrium may contract so much slower than normal and its diastole occur so late that it may still be relaxing during the beginning of left ventricular systole [33] In subjects without mitral stenosis, however the atrium has completed its expansion or relaxation by the time the ventricle starts to contract. Another explanation given for the systolic descent is that it is caused by the pressure drop *in* the thorax secondary to the loss of this blood from the chest due to left ventricular ejection This ignores the increase in thoracic blood volume that occurs during right ventricular systole Flowmeters and angiograms have shown that forward flow into the heart occurs chiefly during right ventricular systole which produces a "suction effect as it draws the floor of the atrium down

The method of referring to this venous systolic

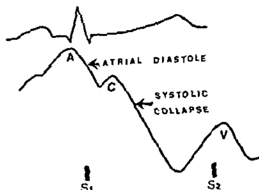


Fig 1 A diagrammatic representation of normal jugular contours as seen in pulse tracings taken with a pickup on the neck

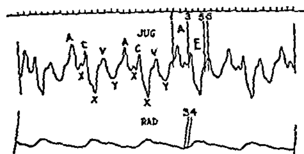


Fig 2 This polygraph recording by Sir James Mackenzie shows the first use of the term X prime in world literature The long distance between the A and C waves was postulated to be due to partial A V block.

collapse during the descent of the base is even more varied than that for atrial relaxation It is left unnamed by at least 14 authors [3-5,7,10,13,14,18,20,23,24,26,27,29] it is called X by at least seven authors [1,2,6,9,11,12,30] it is combined with atrial relaxation under the letter X by at least six authors [2,5,8,21,28,29,34] and it is called X prime (X) by eight authors [15,17,19,22,35,38] Of six authors who called the systolic collapse X" only one named atrial relaxation by some other name and he called it by a name that is used by no one else—he called it Z. [3] The other five had not named the atrial diastolic descent. There were thus at least 16 authors who thought it unnecessary to give a separate name to two separate events

There were nine authors who realized the necessity of naming two different events by two different names. One *however, called the* atrial diastolic descent 'Z and the systolic collapse X." But the letter Z has been used by Paul Wood

Fundamentals of clinical cardiology

The X prime descent in jugular contour nomenclature and recognition

Jules Constant, M D
Buffalo, N Y

That the nomenclature for jugular contours is confused in the literature is shown by the facts that phenomena with different physiologic bases have been referred to by the same name and a multitude of names have been applied to the presystolic and systolic descents This has made the recognition of jugular contours an occult art reserved for those who after years of practice, manage to ignore the confusion in the literature A rational nomenclature is needed before the recognition of jugular contours can be widely taught

The X descent

A review of the probable causes of the jugular contours as seen on a pulse tracing follows

Since jugular contours reflect right atrial contours, we must simultaneously analyze the atrial pulse in order to understand the jugulars Atrial contraction, or systole, signalled by the P wave, produces a rise in atrial and jugular pulse pressure known universally as the A wave Atrial relaxation, or atrial diastole produces the fall in the atrial and jugular pulse that follows the A wave Now we have come to the first conflict in nomenclature (Fig 1) The atrial diastolic descent has been given no name by at least 13 authors,[1 14] has been called X" by at least 14 authors[15 29] and has been called 'Z' by one author[30] Since the majority of writers who named it altogether call it the X descent there is no obvious reason for changing this

The C wave

After atrial systole and diastole the QRS produces ventricular contraction which, in turn first produces a rise in the atrial and jugular contour known as the 'C' wave There are two explanations given for the jugular C wave (1) It is due to bulging upward of the tricuspid valve during isovolumic contraction This is very likely always the cause of the C wave in the atrial pressure curve but not always in the jugular curve Tricuspid bulging contributes to the jugular C wave if there is a delay in onset of left ventricular events as in left bundle branch block or A V block Then the C wave may be bifid with the first part due to tricuspid bulging (2) It is largely due to a carotid artifact on the pulse tracing, i e when isovolumic contraction finishes, and the aortic valve opens the aortic pressure rises and expands the carotid arteries The expansion of the carotid pulse is picked up by the pulse units on the neck which attempt to isolate the jugular pulse

Regardless of any arguments that try to prove that part or all of the C wave in the jugular pulse is due to tricuspid valve bulging most jugular tracings are plagued by obvious carotid artifacts. Mackenzie[23] in 1902, in his book on the pulse was the first to call this the C wave to symbolize the word "carotid" because he believed that it was always entirely a carotid artifact He described an experiment in which pure jugular tracings were taken with the jugular dissected away from the carotid The carotid C wave which had been present before the dissection disappeared after dissection He also described the various amplitudes of C waves that you could obtain by merely varying the pressure or site of your pickup The bulging upward of the tricuspid valve theory was tested and found wanting by Wiggers[14] who described right atrial pressure and jugular pulses taken at various levels and with various types of instruments When he recorded volume changes at successively higher levels from the right atrium to low in the neck,

From the Department of Medicine State University of New York at Buffalo N Y
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Reprint requests to Jules Constant M D The Buffalo General Hospital, 100 High St Buffalo N Y 14203



Fig 5 Since there is a delay in radial pulse when compared with the jugulars, the first of each pair of jugular descents in this subject with atrial fibrillation is the X prime.



Fig 6 A polygraphic curve from a case of auricular fibrillation The ventricular form of venous pulse is displayed, the systolic elements being of plateau form During diastole the venous curve rises gradually and small undulations (f f f) are seen.

diastole Mackenzie in his 1907 article went on to label all his subsequent systolic depressions X.

Sir Thomas Lewis[36] another powerful influence in cardiology used the letter X to label the descent of the base in his 1925 book called *Mechanisms and graphic registration of the heart beat.* His diagram is reproduced in Fig 3 He gave credit to Mackenzie for his jugular nomenclature

Another point in favor of the term X is that it allows us to compromise with those who have taught that X refers to the systolic collapse descent. The letter X is still used, but with a slight modification in order to distinguish the two different hemodynamic phenomena

Historically the X next appears in Best and Taylor s physiology textbook of 1937 Although their illustration referred to Price as its source Frederick W Price s[38] book of 1927 *Diseases of the heart* had many jugular tracings but nowhere was an X mentioned. The course of the X in Best and Taylor s consecutive editions is symbolic of the fate of this nomenclature Up to the sixth edition of 1955[15] the X was described in the text, and a separate drawing as well as an actual pulse tracing with the X and X labeling was used. In the sixth edition, the drawing was omitted. In the seventh edition of 1961 the X had been removed from the text and the only illustration taken from Paul Wood, showed an X placed at the bottom of the systolic collapse descent The writer of that section was no longer Best or Taylor it was one of the many contributors

Fulton s[19] physiology textbook of 1955 now out of print showed the X but in a reproduction of the same tracings as those used by Best and Taylor Zimmerman s first edition of *Cardiac catheterization* had an X' in a jugular tracing in the chapter by Kaplan[22] Although Kaplan referred me to Wiggers as a possible source for the X Wiggers[14] 1923 book *Modern aspects of the circulation in health and disease* which had 22 pages of jugular tracings nowhere showed or even recognized the systolic jugular collapse as a phenomenon separate from atrial diastole The jugular tracing with the X descent was omitted from Zimmerman s second edition

There is, therefore only one modern cardiology book that teaches the use of the X for the systolic collapse due to the descent of the base[17] The only article to appear in the past 60 years that contains a picture of an X was published in 1973 it was co authored by Gibson[37] He had reintroduced the term in 1959 to his colleagues and to me but did not publish his nomenclature

The X atrial fibrillation

Instead of the C wave ending atrial relaxation and beginning the descent of the base the C wave is designated by four authors[2 16 27 29] as merely an "interruption on the X descent Even

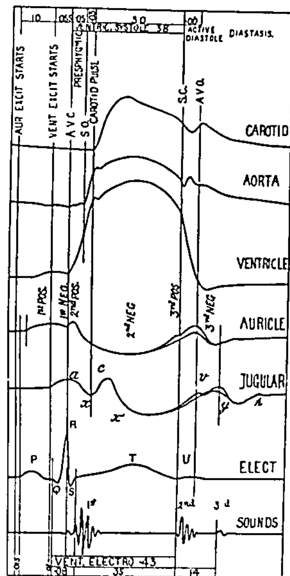


Fig 3 This diagram by Sir Thomas Lewis not only shows an X prime but distinguishes the atrial from the jugular C wave as separate phenomena

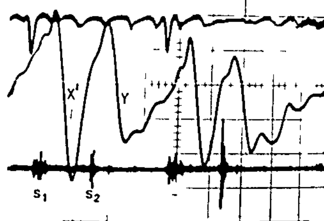


Fig 4 A storage oscilloscope picture taken from an almost asymptomatic 45 year old woman with moderately severe mitral stenosis and a slightly elevated jugular venous pressure The systolic collapse is even greater than the diastolic descent despite atrial fibrillation

for the onset of the A wave and by others for the trough between the A and the C wave [41] Since the atrial diastolic descent has been called X by at least 14 authors we should probably consider Z an unnecessary change Furthermore the letter X has the historical backing of Mackenzie[23] who, in 1902 named the atrial diastolic descent by that letter in his very influential book, *The study of the pulse* in which he described pulse contours and their meanings in 146 pages of kymograph illustrated text Since this book became the most widely quoted source of pulse contour material in the world literature it is probably wise to retain as much of his nomenclature as possible

There were eight authors who named the atrial relaxation descent differently from the descent of the base and who called the systolic collapse X prime This term has several advantages over any other First, there has been no other name given to it by anyone who wanted to distinguish it from the X of atrial diastole Mackenzie,[35] in an article in 1907 showed an X prime on a pulse tracing in apparently the first attempt to distinguish the atrial diastolic descent from a systolic collapse In this article he showed a tracing (Fig 2) with a delay in ventricular contraction due to a first degree A V block The jugular descent during systole was so obviously not due to atrial diastole (which showed its descent long before) that he felt obliged to give a different name and origin for the descent during systole and called it X He described ' the dragging down of the auricular ventricular septum during ventricular systole' as the major cause of the X It is curious how the ambiguity about X and X is seen even while reading Mackenzie s explanation He stated that X is due to the auricular depression but stated further that how much of X is due to the descent of the base is unknown except in A V block He was apparently unwilling to completely contradict his statement in his book of 1902, in which he said flatly that the great fall (X) is due to diastole of the auricle Perhaps he was too much under the influence of the great French cardiologist Potain [39] who in 1867 published the first simultaneous jugular carotid and apex pulse tracings (20 years before Mackenzie did the same thing) and ascribed the systolic jugular descent to atrial

placing the letters X and Y on the troughs began with Mackenzie and it has been carried on with remarkable consistency This has resulted in new definitions of pulse deflections known as the X and Y troughs which have further confused the situation Some authors have actually defined the terms X and Y as representing troughs rather than descents but have gone on to use the terms X and Y as if they were descents [41]

The argument used for naming troughs rather than descents is that since we label waves by placing A C and V on their peaks we should label descents by labeling the troughs This is illogical because a wave consists of a rise and a fall and you cannot label the wave only on the rise or the fall but must place the label on its peak A descent on the other hand, is only one movement i e it is not a fall *and* a rise and so should have its label on the slope of the descent and not at its nadir or trough

Contour recognition by inspection

Normal jugular movements Only now that we have clarified our nomenclature can we describe what is seen on physical examination of the normal jugular pulse Pulse tracings have led us to believe that in the normal jugulars we should be able to see an A C and V wave Only a few authors have stressed the fact that there is a difference between what is recorded in the jugular pulse tracing and what is seen by eye [6,17] Since the C wave in a jugular tracing is mostly carotid artifact *we do not see a C wave* Since it is difficult to separate the X from the X descent by eye these two are usually fused as one descent This X plus X is the total contour seen in most normal adult jugulars when inspection of the neck is carried out by eye (Fig 8) This is because on the right side i e in the right atrium the V wave and subsequent Y descent are very small The reason for this is probably that the right sided V wave is due to a building up of pressure in a very distensible chamber i e the right atrium is too distensible to raise its pressure much when the tricuspid valve is closed.

The descent method of contour recognition One method of recognizing which waves are present is based on three principles (1) it is easier for the eye to see and time descents rather than ascents (2) the descent of the base or X descent, is a systolic event, and therefore must end before the second sound (3) the eye sees movement

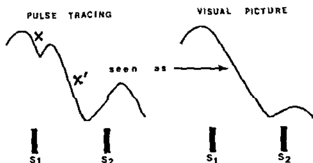


Fig 8 Not only is the X + X usually seen as a single wave (the practised eye can sometimes note a slight interruption on the descent) but with simultaneous auscultation it appears to end at the time of the second sound.

later than the ear hears sound, i e a movement that ends just before a sound appears to end *at* the sound. With the use of these principles it is easy to look for descents or a collapse of a jugular movement that appears to fall on to the second sound If it does then one is seeing an X descent (Fig 8) If the descent does not fall on to the S2 then it must be a Y descent and the wave preceding it must be a V wave

Note that this technique infers which wave is present from the recognition of the *descents* If in the presence of sinus rhythm we see an X descent and very little Y we know that there is a dominant A wave present If on the other hand, we see a large Y and very little X we know that there is a dominant V wave present. If we see an equal X and Y descent we can say that the A and V waves are equal in amplitude

In the presence of atrial fibrillation however an X descent does not imply a preceding A wave since the definition of an A wave requires atrial contraction This therefore is another reason for teaching physicians to both observe and name descents rather than waves It is less confusing to say that there is an X descent with a dominant Y descent in the presence of atrial fibrillation than to describe the waves since in order to describe the waves in a patient with atrial fibrillation and a good X you would have to invent some new terminology for the diastolic wave preceding the systolic collapse

In children and young adults a moderately deep Y descent is commonly present (with the X descent still dominant) This may be because in the young the circulation time may be slightly more rapid than in most adults. Thus, when the A V valves close in systole there is more rapid filling of the atrium than in the adult, and the V

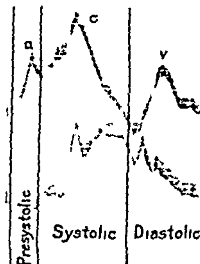


Fig 7 This is a simultaneous jugular and carotid tracing taken by an optical technique The jugular V wave begins at the carotid incisura Note the large C wave due to carotid artifact.

the late Paul Wood [29] doubted that the systolic descent was due to the descent of the base because he thought that it disappeared in atrial fibrillation It is true that in subjects with atrial fibrillation and in heart failure the systolic jugular descent does tend to disappear, probably because of the very poor right ventricular contraction due to both the myocardial damage and the loss of 'atrial kick' However, everyone who does his own jugular tracings must occasionally have seen the jugular systolic descent in the presence of atrial fibrillation (Fig 4)

Mackenzie [10] in his 1913 book, *Diseases of the heart* showed a systolic descent in atrial fibrillation which he labeled X He showed a tracing of the same patient at another time, still in fibrillation in which the X had disappeared Sir Thomas Lewis[36] clarified the problem in his 1925 book, *The mechanisms and graphic registration of the heart beat* where he noted that in atrial fibrillation curves obtained from patients in whom venous engorgement is absent or slight are similar in their systolic phases to the curves of normal subjects He then showed Fig 5 as an example He stated, 'In cases where the heart is engorged and the veins overfilled the first depression, corresponding to the X in normal curves becomes more or less filled until in advanced stasis the curve assumes a prominent plateau form" He used Fig 6 to illustrate this

The V wave and Y descent

The remainder of the normal jugular and atrial tracing shows a wave during systole that is due to atrial filling while the A V valves are closed, i e, the drop in atrial pressure due to the descent of the base is overcome somewhere in midsystole by filling from the veins entering the atrium This wave is universally called the V wave Since it occurs during systole, it should be considered a *systolic* event, just as is the X descent. There are those who teach however that the V wave is a diastolic event! It is true that it ends shortly after the A2 and therefore ends in early diastole but it does not add to our clinical understanding of the V wave which is entirely dependent on closed A V valves to call it a diastolic event. The blame for calling the V wave a diastolic event rests squarely with Wiggers [11] who showed a pulse tracing which was so full of carotid artifact that indeed the V wave did start at the time of the dicrotic notch of the carotid pulse (see Fig 7) This tracing was taken by an optical technique which includes marked carotid artifact It is strange that even though Wiggers realized the presence of carotid artifact, and did publish tracings of volume curves of the jugular and atrial pulse that have V waves beginning long before the dicrotic notch, he still insisted that the V wave *begins* in diastole

Some authors also claimed that the V wave is *due* to ventricular contraction and gave that as a reason for calling it a V wave [26] This is a confusing concept because, although the V wave does occur mainly during ventricular contraction it is really built up *in spite of* ventricular contraction i e, in spite of the pressure drop due to descent of the base caused by ventricular contraction

When ventricular systole ends and the ventricular pressure drops to below atrial pressure the A V valves open and the rise in atrial pressure that caused the V wave comes abruptly to an end The atrial pressure then falls rapidly to produce a drop in the pulse tracing known universally as the 'Y descent' ever since Mackenzie gave it that name The atrial and ventricular pressures now ride together in diastole and, if diastole is long enough another wave is produced known as the 'H wave (after Hirschfelder who first described it)

Trough labeling problems

Even when proper labeling of descents is used there is a traditional practice of placing the letters at the bottom or nadir of the descents rather than beside them (Figs 2 and 3) The practice of

placing the letters X and Y on the troughs began with Mackenzie and it has been carried on with remarkable consistency This has resulted in new definitions of pulse deflections known as the X and Y troughs which have further confused the situation Some authors have actually defined the terms 'X and Y as representing troughs rather than descents but have gone on to use the terms X and Y as if they were descents [41]

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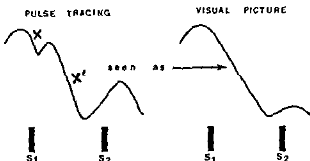


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wave being a systolic event, becomes taller In the adult, a prominent Y descent, which implies a prominent V wave, should be considered as probably abnormal, and an explanation for it should be sought, such as double filling of the right atrium during systole via an atrial septal defect.

With proper nomenclature and the avoidance of artifact laden pulse tracing teachings we can train physicians to recognize the normal jugular pulse contour by mere inspection of the neck This should make it possible to better understand and teach how to recognize abnormal jugular contours and there are many texts and articles in which this information is available

Summary

To help prevent the inspection of jugular contours from falling into disuse due to an irrational nomenclature tradition the historical background for the development of a bewildering jugular nomenclature is presented The term 'X prime' is revived in an attempt to bring order into the labeling of the systolic venous collapse The descent of the base is shown to produce an X prime descent even in the presence of atrial fibrillation Labeling troughs rather than descents is examined in an attempt to discourage this firmly entrenched tradition Finally an audiovisual method of recognizing the normal jugular contour is presented utilizing the observation that the X prime descent falls on to the second heart sound

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Electrophysiology and pharmacology of cardiac arrhythmias I Cellular electrophysiology of the mammalian heart

Michael R Rosen M D*
Andrew L Wit, Ph D*
Brian F Hoffman, M D
New York N Y

An understanding of the mechanisms underlying the genesis of cardiac arrhythmias and how they are influenced by antiarrhythmic drugs requires some knowledge of the electrophysiology of normal cardiac fibers Although the basis for our knowledge of electrophysiology has been provided by a variety of techniques the use of intracellular microelectrodes has particularly facilitated the study of the transmembrane electrical activity of single cardiac fibers and has provided much of the recent information on the mechanisms responsible for cardiac arrhythmias and antiarrhythmic drug action Our intent here is to summarize the ionic and electrophysiologic basis for the normal cardiac action potential In subsequent sections we will discuss derangements of normal electrophysiologic function, their implications with regard to the initiation of arrhythmias and the effects of various therapeutic modalities on cardiac cellular electrophysiology and function

Microelectrode techniques for recording cardiac transmembrane action potentials The tip diameter of glass capillary microelectrodes is sufficiently small (< 1 μ) to permit their insertion through the cardiac cell membrane without causing demonstrable injury [1] Once cardiac cells have been impaled with such electrodes it is possible to record electrophysiologic events over relatively long periods of time Observations can be made of the electrophysiologic properties of tissues from normal or diseased hearts, and of the effects on these properties of various interventions, such as perfusion with antiarrhythmic drugs. The cardiac tissues studied are either permitted to beat spontaneously or are stimulated electrically through intracellular or extracellular electrodes

The cardiac resting membrane potential When the tip of a glass microelectrode is advanced into a cardiac cell the potential difference between this intracellular electrode and a reference electrode in the extracellular space can be recorded (Fig 1) For most cardiac fibers the inside of the cell is 80 to 90 mV negative with respect to the extracellular space This transmembrane potential recorded during a period of electrical quiescence is referred to as the resting membrane potential It is largely due to a concentration gradient for potassium ion across the cell membrane which is maintained by energy requiring active transport [2,3] Because of active inward transport of potassium and outward transport of sodium the intracellular potassium concentration is thirty times higher than the extracellular potassium concentration and the intracellular sodium concentration is low with respect to the extracellular value [1]

At rest, the membrane is permeable mainly to potassium ion and as a result the resting membrane potential is a linear function of the logarithm of the extracellular potassium concentration over a wide range (Fig 2) However, if the extracellular potassium concentration is less than 5 mM, the slope describing the relationship between potassium concentration and resting

From the Department of Pharmacology Columbia University College of Physicians and Surgeons New York N Y
Received for publication April 26 1974
Reprint requests to Dr Michael R Rosen Department of Pharmacology College of Physicians and Surgeons 630 W 168th St. New York N Y 10032
Drs Rosen and Wit are Senior Investigators of the New York Heart Association Dr Rosen is a Research Fellow of the John Polachek Foundation

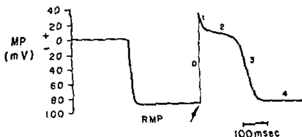


Fig 1 Electrical recording during insertion of a microelectrode into a myocardial cell. When the electrode tip is outside the cell a steady level of 0 potential is recorded. When the microelectrode tip is advanced into the cell an electronegative transmembrane potential is recorded. This is the resting membrane potential (RMP) An appropriate stimulus (arrow) initiates an action potential See text for discussion

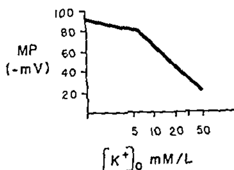


Fig 2 Effect of extracellular potassium concentration ([K]o) on the resting membrane potential (MP) of human atrial cells. Modified after Gelband and co-workers[17] See text for discussion

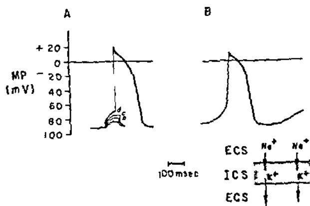


Fig 3 Excitability and automaticity of a cardiac cell. *Panel A* excitability *a*, *b* and *c* represent depolarizing pulses that have been applied to a cardiac cell through an intracellular microelectrode Although sufficient to displace membrane potential, this displacement does not reach threshold potential and the cell subsequently repolarizes The depolarization indicated by *d* does bring the membrane potential to threshold potential and as a result there is a propagated action potential *Panel B* Automaticity spontaneous phase 4 depolarization results in attainment of threshold potential by a cell in the specialized conducting system. As a result, a propagated action potential occurs. In the lower diagram are the ionic events which may initiate phase 4 depolarization in Purkinje fibers ICS = intracellular space ECS = extracellular space A steady flow of positive charge is carried into the cell by sodium ion (Na^+) Positive charge is carried out of the cell by potassium ion (K^+) During phase 4 the outward positive current decreases, resulting in an accumulation of positive charge inside the cell and gradual depolarization.

membrane potential is far less steep than at higher concentrations[1]

The cardiac action potential The resting potential of a cardiac fiber is maintained until the cell is excited by an electrical stimulus originating from an external source or from an action potential (Fig 1) Excitation and the elicitation of an action potential occur if a depolarizing stimulus lowers the transmembrane potential of an adequate area of membrane rapidly enough from resting to threshold potential The latter is a critical level of membrane potential at which regenerative depolarization is initiated[4] The rapid depolarization or upstroke of the action potential is referred to as phase 0 (Fig 1) This is followed by three phases of repolarization a relatively rapid repolarization (phase 1) a plateau (phase 2) and a subsequent return (phase 3) to resting membrane potential The period between action potentials is referred to as phase 4

Specific currents carried by different ions have been identified as being responsible for the voltage changes which occur during the course of the action potential The resting cell is quite permeable to potassium and relatively impermeable to sodium ions[1] When membrane potential is decreased to the threshold level sodium permeability increases markedly and a rapid inward flux of sodium ion referred to as a sodium current results in phase 0 depolarization[5] This is largely complete in several milliseconds. The subsequent phase 1 repolarization has been attributed to an inward current carried by chloride ion[6] During the plateau, two ionic currents maintain a fairly steady membrane potential. These are the decreasing inward sodium current and, in some cells an inward calcium current[7] During phase 3, positive charge is carried from the cell by an outward potassium current, resulting in a return to resting membrane potential[8]

Cardiac impulse initiation The excitability of

cardiac cells may be expressed in terms of the current required to depolarize membrane potential to the level of threshold potential (Fig 3, A) As the difference between membrane potential and threshold potential is increased, a greater stimulus current is needed to displace membrane potential to threshold Similarly, the smaller the difference between membrane potential and threshold potential the smaller the current required to attain threshold Stimulus currents of insufficient magnitude to displace membrane potential to threshold will induce transient, low amplitude depolarizations (Fig 3 A) which then return to resting membrane potential, rather than regenerative action potentials

Certain cells of the cardiac specialized conducting system (sinus node atrial specialized conducting fibers the lower or N H region of the atrioventricular node and the His Purkinje system) not only are capable of initiating action potentials in response to adequate stimuli but may depolarize spontaneously during phase 4 [1] In such instances if threshold potential is attained a spontaneous action potential may be initiated This phenomenon is referred to as automaticity (Fig 3 B) In the normally functioning heart, phase 4 depolarization in the sinus node results in the fastest rate of impulse initiation and the sinus node hence serves as the cardiac pacemaker

The ionic events responsible for phase 4 depolarization are only partly understood Immediately following repolarization potassium conductance of the cell membrane is high and there is a large outward potassium current [9] Potassium permeability and the outward potassium current then decline with time during phase 4 There is also a small inward sodium current during phase 4 which does not change appreciably with time [10, 11] The concurrence of a decreasing positive outward current (potassium) and a steady positive inward current (sodium) results in a gradual drift of membrane potential toward less negative values seen as phase 4 depolarization As the level of threshold potential is approached there is a voltage dependent increase in sodium conductance resulting in initiation of phase 0 depolarization and a regenerative action potential [10, 11]

The greater the slope of phase 4 depolarization the faster the rate of impulse initiation by a pacemaker cell This however, is not the only factor which modifies the rate of impulse initiation Any event which brings membrane potential closer to threshold (such as a decrease in membrane potential at the onset of phase 4 depolarization) will increase the pacemaker rate. Conversely, events which decrease the slope of phase 4 or move membrane potential away from threshold potential will tend to slow pacemaker rate

Cardiac impulse propagation After an impulse is initiated in the sinus node it is propagated through the specialized conducting system to the atrial and ventricular myocardium The activation of atrial and ventricular myocardium respectively, give rise to the electrocardiographic P wave and QRS complex The velocity with which an activating waveform propagates through the heart is dependent on a number of factors including the passive or cable properties of the cardiac fibers Both the cardiac cytoplasm and the extracellular fluid have low resistances and are good conductors of electrical current Interposed between them is a cell membrane which at rest has a relatively high resistance and which is an electrical capacitor [1] When an area of membrane is excited its membrane potential changes rapidly This depolarized membrane is adjacent to normally polarized membrane which has not yet been excited. Current then flows between the excited and unexcited portions of the membrane depolarizing the latter areas to threshold and resulting in propagation of the action potential [1]

Conduction velocity also is dependent on the action potential characteristics of cardiac cells Generally cells which maintain higher levels of resting membrane potential (such as Purkinje fibers) initiate action potentials of higher amplitude and more rapid phase 0 upstroke velocity (V_{max}) and conduct impulses more rapidly than cells with lower resting membrane potentials such as those in the atrioventricular node [1] As a general rule as resting membrane potential for a cell is increased over a wide range of values (approximately −55 to −85 mV) there is a progressively greater inward sodium current during phase 0 resulting in increases in action potential amplitude and maximum upstroke velocity of phase 0 (V_{max}) [5] The relationship between membrane potential and action potential amplitude is illustrated in Fig 4 It is apparent from this figure that as action potentials are ini

tiated at progressively lower membrane potentials the amplitude (and overshoot) diminishes and the time to reach peak amplitude is prolonged.

The level of threshold potential further modifies propagation The greater the difference between threshold potential and membrane potential at the time an impulse is initiated the greater the stimulus required and, at times the longer the time interval required to lower membrane potential to threshold and initiate an action potential Hence changes in the interrelationship of threshold potential and resting membrane potential[12] as well as alterations in action potential amplitude and V_{max} can change the velocity of propagation of the cardiac impulse

Membrane responsiveness ' Membrane *responsiveness* is defined as the relationship of the maximum upstroke velocity of phase 0 (V_{max}) of an action potential to the level of membrane potential at which the action potential is initiated (Fig 5) It provides information concerning the ability of a cell to respond to a stimulus at different levels of membrane potential Because of the V_{max} is a *determinant of conduction velocity* the membrane responsiveness curve also indicates indirectly whether conduction velocity of an action potential elicited at any level of membrane potential will be altered by a given intervention For example if the entire responsiveness relationship is shifted to the right on the voltage axis or depressed (dotted curve Fig 5) as it might be by a pharmacologic agent, this suggests that conduction will be slowed. Similarly in situations where conduction is initially depressed the administration of an agent which shifts the responsiveness curve to the left on the voltage axis or elevates it, would be expected to result in an enhancement of conduction

Refractory periods Once an action potential has been elicited cardiac cells will not initiate an action potential in response to a second depolarizing stimulus until repolarization to at least −50 mV has occurred (Fig 6 *A*) The effect of a stimulus at this voltage level may be to displace membrane potential transiently (response a) without initiating a propagated action potential. The earliest transient depolarization which can be elicited defines the end of the absolute refractory period for that cell[14] A stimulus applied at −55 to −60 mV will result in an action potential that may *propagate along the fiber*

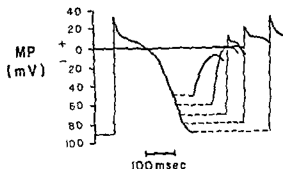


Fig. 4 Relationship of action potential amplitude and upstroke velocity to the membrane potential at which the action potential was initiated. A single control action potential is depicted as are a series of action potentials originating at progressively lower (less negative) levels of membrane potential *during repolarization* As membrane potential at which each action potential is initiated decreases the action potential amplitude and overshoot decrease in magnitude as does the upstroke velocity of phase 0

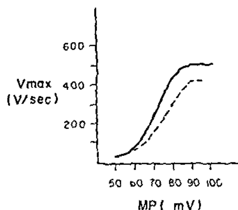


Fig 5 Membrane responsiveness The maximum upstroke velocity of phase 0 for a series of action potentials (V_{max}) is depicted as a function of the membrane potential (MP) at which the action potentials were initiated The relationship is that of a sigmoid curve (solid line) Any intervention which depresses the curve (broken line) would be associated with a decrease in V_{max} for any level of membrane potential As a *general rule those interventions* which depress responsiveness would be expected to slow conduction and those which enhance responsiveness would be expected to accelerate conduction.

bundle (b) The earliest propagated action potential that can be elicited defines the end of the effective refractory period.[1]

The duration of effective refractory periods is not uniform throughout the cardiac conducting system. Three sites have thus far been identified which have effective refractory periods longer than those of nearby cells and thus seem to alter

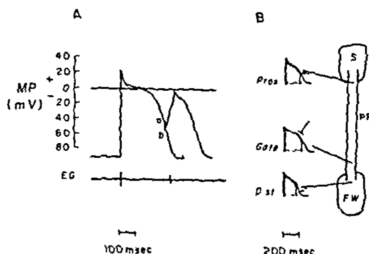


Fig 6 *A* the absolute and effective refractory periods of a cardiac fiber Response *a* delineates the end of the absolute refractory period, *b* the end of the effective refractory period. *EG* is an electrogram recorded from the fiber bundle distal to the microelectrode impalement See text *B*, The gate proximal gate and distal action potentials recorded in a Purkinje fiber bundle (PF) between the ventricle septum (VS) and free wall (FW) are shown The action potential duration and effective refractory period (shaded area) are longer at the gate than proximally or distally As a result premature depolarizations which propagate in the proximal or distal conducting system (arrows) may arrive at the gate while it is still refractory and, therefore not activate the remainder of the conducting system (See text for discussion)

propagation of prematurely delivered or rapidly repetitive cardiac impulses These sites are the ventricular gate [15] the atrioventricular node,[1] and the atrial perinodal fibers [6]

The gate is a site in the distal Purkinje system at which the action potential duration and the effective refractory period are longer than at more proximal or distal locations [15] Premature action potentials initiated proximal or distal to the gate after termination of the local effective refractory period may propagate to the gate but not traverse it because of the greater duration of the refractory period here (Fig 6, *B*) Hence the functional refractory period for the distal ventricular conducting system will be determined in part by the effective refractory period at the gate

As Purkinje fibers approach their terminal insertion into the myocardium they arborize into multiple branches in each of which there is a gate In normal situations the action potential duration and the effective refractory period at all these gates would be expected to be approximately equal If they are unequal the duration of the effective refractory period at the shortest gate will determine the functional refractory period for the ventricle As shall be explained in a subsequent section if there is sufficient inequality of action potential duration at different gates the occurrence of re entry may be facilitated.

In the atrium, perinodal fibers have been described surrounding the sinus node [16] These fibers serve a gate like function with regard to the sinus node and the remainder of the atrial specialized conducting system Hence the propagation of premature depolarizations between the atrium and sinus node is limited by the effective refractory period of the perinodal fibers Under appropriate conditions conduction of premature depolarizations through the perinodal region may be sufficiently slow to contribute to re entry

The final area to be considered with regard to refractoriness is the atrioventricular node Conduction through this site proceeds more slowly than that through the atria and ventricles This is, in part a function of the low action potential amplitude and V_{max} of atrioventricular nodal cells [1] It is also a reflection of the fiber geometry of the atrioventricular node, in which there are multiple arborizations of the specialized conducting fibers and rather narrow fiber diameters as compared to other sites in the conducting system. All these factors contribute to the slowing of conduction

At increasing rates of stimulation the duration of the action potential and effective refractory period of most types of cardiac fibers decreases however, increases in stimulus rate have a far less pronounced effect on the duration of the atrioventricular nodal effective refractory period.[1] Hence, as rate accelerates the atrioventricular nodal effective refractory period shortens less than at nearby sites in the heart or does not shorten at all and progagation of impulses across the node may be blocked. This characteristic of atrioventricular nodal electrophysiology permits it to limit the propagation of impulses between the atria and ventricles.

Effects of autonomic mediators on cellular action potentials *1 Catecholamines* Sympathetic nerve stimulation and/or catecholamine release will modify the electrophysiologic properties of cells in the atrial and ventricular myocardium

and specialized conducting system Catechol amines increase the slope of phase 4 depolariza tion in sinus node and specialized conducting cells and may thereby enhance automaticity in these sites[1] If cells are partly depolarized and conduction velocity is lower than normal cate cholamines may hyperpolarize the cells in crease action potential amplitude and V_{max} and accelerate conduction[1]

2 *Acetylcholine* Acetylcholine is the neu rotransmitter which mediates the effect of vagal stimulation on the heart It modifies electrical activity in the sinus node atrium and atrial and atrioventricular junctional specialized conduct ing system Acetylcholine decreases the slope of phase 4 depolarization of sinus node and atrial specialized conducting cells thereby slowing not only the spontaneous rate of the sinus pacemak er but of other potential pacemakers in the atrial and junctional regions[1] Acetylcholine also hyperpolarizes atrial cells, an effect associated with enhanced intra atrial conduction

In the atrioventricular node acetylcholine decreases action potential amplitude and the V_{max} of phase 0[1] The effect on phase 0 may be so marked as to fragment the upstroke into several distinct components These actions which occur with little or no change in resting membrane potential contribute to a slowing of conduction in the atrioventricular node In addi tion acetylcholine prolongs the atrioventricular nodal effective refractory period[1]

Conclusion

In this section we have reviewed some of the factors responsible for normal cardiac impulse initiation and propagation In future sections we shall discuss the events which predispose to the occurrence of arrhythmias and their modifica tion by pharmacologic agents.

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Hepatitis as a hemodialysis hazard

Hemodialysis and kidney transplantation have produced remarkable prognostic improvement for patients with chronic renal disease. Tempering this success, however, has been an attendant increase in serious bacterial and viral infections due in part to the complex instrumentation of uremic or immunosuppressed patients as well as to the difficulty in adequately sterilizing dialysis equipment. Particularly recalcitrant among these infections has been viral hepatitis. In one report[1] only septicemia and bacterial pneumonia surpassed viral hepatitis as major infective causes of death in chronic dialysis patients. In a study of 65 hemodialysis units conducted by the Center for Disease Control during the years 1967-1970, 82 per cent of participating units reported hepatitis in patients, staff, or both. The incidence of infection in 1970 for center-based patients and staff was 4.4 and 3.4 cases, respectively, per 100 persons at risk.[2]

Because the majority of hepatitis epidemics in dialysis units have been etiologically linked to the type B (long incubation) hepatitis virus, studies utilizing the Australia antigen (hepatitis B antigen, HBAg) as an immunologic marker have permitted more effective investigation of hemodialysis-associated hepatitis. Despite the availability of this tool, little is known about the epidemiologic patterns and modes of transmission of hepatitis B within this environment. Particularly sparse has been knowledge of its mild or asymptomatic forms which appear to be not only clinically significant in terms of late sequelae but which also comprise a significant reservoir of infection for patients, staff, family members of each, and presumably the entire community. With recent development of sensitive methods for detection of homologous serum antibody (HBAb), a more efficient marker for assessing prevalence of hepatitis B infection, it has now become possible to clarify the epidemiology of dialysis-associated hepatitis.

Utilizing radioimmunoassay, the most sensitive of available techniques for detection of both HBAg and HBAb, we have serologically quantitated the prevalence of hepatitis B infection in four hemodialysis units without prior epidemics of clinical hepatitis.[3] Thirty-four per cent of patients and 36 per cent of staff were seropositive for HBAg or HBAb (compared to 14 per cent of non-dialysis-associated healthy controls, $p < 0.001$). Six per cent of asymptomatic dialysis patients (45 per cent of those with prior history of icteric hepatitis) were HBAg positive, confirming that chronically uremic patients frequently become persistent carriers of HBAg, presumably because of altered immunologic competence associated with this disease state. Among patients, transfusion of blood products, total duration of dialysis therapy, and frequency of individual dialyses showed a positive association with infection prevalence. For staff, serologic evidence of infection was correlated by occupational category with degree and intensity of exposure to equipment and material utilized in dialysis procedures. In this group lengthening duration of dialysis unit exposure was also associated with increasing hepatitis B infection prevalence, but little change was apparent after 18 months of total dialysis unit exposure. Other risk factor analysis demonstrated glove-wearing to be clearly protective for personnel engaged in dialyzing: 57 per cent of those who never adhered to this precaution were seropositive, compared to 29 per cent of those who occasionally wore gloves, and 22 per cent of those who always complied with this measure. While accidental needle pricks are alarmingly frequent among dialysis personnel, this factor did not clearly correlate with infection prevalence. Furthermore, the rapidity of exposure (27 per cent of staff were seropositive after six months of employment on the unit) and the apparent plateau after 12 to 18 months imply not only that contact with the infectious agent is immediate and intense but also that transmission is highly efficient within the dialysis environment.

It is therefore apparent that while both endemic and epidemic proportions of dialysis-associated hepatitis B have now been documented, the precise mechanisms of disease transmission remain to be elucidated. The possibility of spread of the infectious agent via body fluids other than blood is still unclear; the potential routes of transmission are equally hazy. Apart from the obvious exposures from blood transfusions, accidental needle pricks, or other forms of tissue penetration, the potential role of mucous membrane contamination, blood spillage over intact skin (including subsequent hand to mouth transfer), aerosolization of blood and other theoretical mechanisms of transmission need documentation. Recent studies have demonstrated not only the stability of HBAg on various environmental surfaces[4] but also its seeming ubiquity in the dialysis unit environment.[5] These findings support the concept that exposure to the infectious agent within the dialysis unit can occur by other than obvious parenteral means and that the immediate intramural environment may constitute important modes and reservoirs for disease transmission.

While availability of a vaccine for type B hepatitis looms in the near future,[6] its safety and effectiveness in individuals with immune deficiency will merit intense scrutiny. At present, the firm documentation of potential methods of disease transmission through careful epidemiologic studies offers the greatest hope for alleviating a serious problem in the therapy of chronic renal disease.

Charles P. Pattison, M.D.
Medical Epidemiologist
Phoenix Laboratories
Center for Disease Control
U. S. Public Health Service
4402 N. 7th St.
Phoenix, Ariz. 85014

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The action of vitamin C on blood vessels

The relationship between vitamin C fat and blood vessels is now becoming much clearer

Zaitsev Myasnikov and Sheikman,[1] in 1964 gave animals an atherogenic diet containing ^{14}C labelled cholesterol and showed that the cholesterol was deposited on the aorta If however the animals were given vitamin C as well as the diet, the cholesterol was found in the liver and the adrenals but not on the aorta. Thus vitamin C is responsible for the transport of cholesterol to the liver

Personal observations[2] that in young healthy people the serum cholesterol went down after the administration of vitamin C while in atherosclerotic patients it tended to rise suggested that this was due to mobilization of arterial choles terol and in effect confirmed the Russian experiment in human subjects. Sokoloff Michiteru, and Saelhof[0] treated elderly atherosclerotic patients with vitamin C over a 2½ year period, and was able to produce striking improve ment in the patients clinical condition without making much impression on the serum cholesterol thus supporting the hypothesis that the arterial cholesterol was being mobilized with resulting circulatory improvement.

An isolated serum cholesterol determination is therefore of no value because it gives no indication of the state of the ar teries. Of much greater value would be the study of the behavior of the serum cholesterol after vitamin C because this would give some indication of the amount of cholesterol on the arteries. However this is really academic because the important factor is that while vitamin C is being given, the cholesterol is being directed away from the arteries.

Vitamin C also acts on the other components of fats. It reduces the β lipoproteins [1] enhances the activity of lipopro tein lipase and therefore brings down the triglycerides.[3] In addition to this, it provides the ground substance for the blood vessel walls. In other words, it has a controlling in fluence on all the factors which become abnormal in ath erosclerosis.

Thus a balance exists between vitamin C and fat. If the balance permanently favors vitamin C the cholesterol will always be delivered to the liver the β lipoproteins will re main low the lipoprotein lipase activity will be high, so the triglycerides will be low and the arteries will be well sup plied with ground substance so they will remain clean. If on the other hand, the balance favors the fats, there will be a gradual accumulation of cholesterol in the arteries, the other fat fractions will gradually become abnormal and the ar teries will lose their ground substance so atherosclerosis will result.

The difficulty in proving any hypothesis relating to atherosclerosis however logical it may be is very great because of the widespread incidence and insidious onset of the disease No adult can be guaranteed to be normal and there is no absolute method of demonstrating normality"

However the same cannot be said of the veins Deep vein thrombosis has a very similar epidemiologic distribution to atherosclerosis, and it has two advantages over the arteries where studies are concerned the shortness of the time ex posure to risk and the convenience of methods for studying the development of thrombi

A double blind trial has been done[4] on patients who were vulnerable to a deep vein thrombosis using vitamin C (1 Gm. daily) and a placebo ^{125}I fibrinogen was used to detect the development of thrombi The incidence of deep vein throm bosis in the vitamin C group was halved as measured by this method, but what was much more striking was the reduction in physical signs This was a reflection of the marked reduc tion in the degree of radioactivity found in the positive legs in the vitamin C group and therefore in the extent of the thrombus A rise of more than 15 per cent was regarded as positive but six of the vitamin C patients had rises of less than 25 per cent and were therefore only just in the positive range None of the vitamin C patients had a rise of more than 80 per cent while several of the placebo patients had rises of more than 200 per cent

Vitamin C therefore has a powerful antithrombotic effect Whether this action is directly on the coagulation system or a consequence of its action on the blood fats, is a matter for speculation and study Carnivorous animals, which syn thesize their own vitamin C are not troubled with atherosclerosis or other thrombotic disease and yet their coagulation system is, if anything more active than ours[5] This would suggest that in man the action of vitamin C is ini tially on the abnormal blood fats and then indirectly on the coagulation system.

The protective action is a rapid one In the study described above the patients were divided into three main groups Pa tients for hip arthroplasty were given vitamin C from the time they were seen in the outpatient department and up to six weeks treatment was given (average 15 days) Patients

having a prostatectomy received vitamin C after admission and had an average of seven days preoperative treatment. Patients who had a coronary thrombosis did not have their vitamin C until after the catastrophe had occurred. Although the numbers were small there was virtually no difference in the degree of protection afforded by vitamin C in the three groups.

Thus provided that the vitamin C is given as quickly as possible after people are admitted to hospital with a condition which exposes them to a deep vein thrombosis they should be protected. The trial has now been followed up by the administration of vitamin C routinely in our surgical and orthopedic wards and deep vein thrombosis has now disappeared from these wards.

Andrews and Wilson[6] giving 200 mg of vitamin C daily to geriatric patients found that it did not provide any protection against thrombotic disease. Sokoloff and associates,[3] giving 1 to 3 Gm daily to elderly atherosclerotic patients, were able to protect all their 60 patients for up to 2½ years (i e the end of the trial) from further thrombotic episodes. Routine administration of 500 mg daily to our surgical patients produced a very occasional case of deep vein thrombosis, but since we have increased the dose to 1 Gm daily we have had no further cases. This suggests that in the elderly and most vulnerable cases at least 1 Gm daily is needed to provide protection against thrombotic disease.

There are certain points of interest which should be mentioned (1) Smokers have lower vitamin C levels than non smokers[7] (2) A man who has had a coronary thrombosis is almost invariably told to lose weight. His low calorie diet contains an abundance of vitamin C–containing foods (3) Women who take contraceptive pills have a lowering of their vitamin C levels.[8]

Thus, vitamin C protects the capillaries by a direct action on the vessel walls. Its protective action on the veins and the arteries is a combination of its action on the vessel walls and the blood fats, with an indirect action on the coagulation system. The capillary defect is an acute deficiency while thrombosis is a long term negative balance of vitamin C.

C. R. Spittle M.R.C.Path.
Pathology Department
Pinderfields Hospital
Aberford Rd.
Wakefield, Yorkshire England

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Some aspects of the left atrial sound

The atrial sound is the presystolic vibration associated with atrial systole. It is also known as the fourth sound but this term is confusing since it is the initial sound of the complete cardiac cycle. It is a low frequency vibration between 25 and 100 Hz, and usually near the threshold of human hearing. The peak vibrations of the atrial sound coincide with the peak of the atrial beat (the a wave of apex displacement) which is the outward movement of the left ventricular apex caused by left atrial contraction. The time relationship of the atrial sound with the P wave of the electrocardiogram is variable and incompletely understood. When an atrial sound is recorded in the normal subject it usually occurs at about 0 12 to 0 16 sec after the onset of the P wave. In patients with heart disease the interval may be shorter or longer than this but never less than 0 07 sec. The more severe forms of left ventricular disease are associated with shorter intervals.[1] Recovery of heart function after myocardial infarction[2,3] and with the treatment of hypertension[4] leads to progressive lengthening of the interval between the P wave and the atrial sound, which may become incorporated in the first sound.

The atrial sound is best detected by examining the patient in the left lateral position. In cases with a pathological atrial gallop it is often easier to feel the atrial beat with the fingers on the cardiac apex than to hear it. The sound is most easily heard with the bell of the stethoscope placed very lightly over the cardiac apex and is usually filtered out by firm pressure which converts the skin of the chest wall into a diaphragm.

The healthy young ventricle fills readily in early diastole with a prominent rapid filling wave of apex displacement often accompanied by a physiological third heart sound. The atrial contribution to ventricular filling is relatively small, the a wave of apex displacement is small and any accompanying sound vibrations are inaudible clinically. The diseased left ventricle fills less readily in early diastole, the rapid filling wave is attenuated and the physiological third sound is lost while the contribution from left atrial systole increases producing a large apical a wave often accom

panied by an audible atrial sound. Further deterioration in heart function exaggerates this pattern. However in severe disease with left heart failure and raised left ventricular mean diastolic pressure the early diastolic rapid filling wave returns a pathological third sound (ventricular gallop) is acquired, while the "a" wave and atrial sound diminish.[5 8]

Such changes are well demonstrated by apexcardiography. It is traditional to measure the "a" wave amplitude as a ratio of the total apex displacement.[7,9] However in view of the reciprocal nature of the early and late phases of ventricular filling it seems to us more logical to compare the "a" wave amplitude with the total *diastolic* excursion of the apexcardiogram.[8] This also allows the apexcardiogram to be amplified, cutting off the peak of the systolic outward movement, to display the diastolic events more clearly.

The atrial sound and the third sound have many similarities and probably have a common origin. Both occur at the end of a rapid filling phase of the ventricle at the peak of an outward movement of the ventricular apex. They have similar frequency characteristics they are both enhanced by maneuvers which increase ventricular filling and when they occur in disease they appear to represent exaggerations of normal physiological events. It is likely that both are generated by the sudden tension in the mitral cusps and chordae tendineae which occurs when the left ventricular apex and mitral annulus are carried abruptly apart by rapid filling of the ventricle.[10 11] Involvement of the mitral valve apparatus in the production of the third sound is demonstrated by the findings in mitral incompetence. In rheumatic cases, where the cusps and chordae are present the rapid filling wave and third sound are prominent,[11] whereas in severe regurgitation around a prosthetic mitral valve the filling peak and third sound are rudimentary[12] or absent.[13]

At least three separate components of the atrial sound have been recognized.[14] Phonocardiograms recorded from microphones in the esophagus[14] or left atrium[15] have shown low frequency vibrations occurring 0 04 to 0 06 sec after the onset of the P wave and this component is not detectable at the chest wall. It has been attributed to left atrial contraction. In complete heart block two further components of the atrial sound are usually recordable at the cardiac apex.[16-18] The first of these occurs 0 07 to 0 14 sec after the onset of the P wave its maximum vibrations coincide with the peak of the apical "a" wave and it is lost when the left atrium contracts against a closed mitral valve during ventricular systole.[19] We believe that this component is the same as the atrial sound which is heard and recorded in sinus rhythm and whose frequency characteristics are very similar. The second of the apical components of the atrial sound occurs at about 0.20 to 0 28 sec after the onset of the P wave well after the peak of the "a" wave and is also lost when the left atrium contracts during ventricular systole. Its significance is uncertain. We do not agree with the widely held belief[18,20] that the first apical component is an "inaudible vibration" (it is frequently louder than the second component) retained during ventricular systole and caused by left atrial contraction, and that it is the second apical component which corresponds with the atrial sound of sinus rhythm.

Many clinicians in the past have regarded any audible atrial sound in an adult as a sign of heart disease.[21,22] However Potain's[23] original observation that the sound may be heard in health is now being confirmed.[24,25] It has long been recognized that the atrial sound can be a normal finding in childhood,[26] where the circulation is brisk and the chest wall thin, but the normal relationship between the large rapid filling wave and the small "a" wave of apex displacement is retained. In hyperdynamic and hypervolemic states the detectable diastolic events are amplified without disturbing this relationship and the atrial sound vibrations may become loud enough to be heard. In adult life the incidence of an atrial sound in apparently normal subjects increases with age[27] from being extremely rare below forty to comparatively common in the very old.[28] This increasing incidence may be caused by the aging mitral valve apparatus becoming more productive of noise[29] by a change in the pattern of left ventricular filling with age or by an increase in the incidence of occult heart disease probably all three factors contribute. In the apparently healthy middle aged subject the pattern of left ventricular filling events as traced by the apexcardiogram may help to decide whether an atrial sound is physiological or pathological. When the "a" wave is small in comparison with a brisk rapid filling wave it is reasonable to regard the atrial sound as a physiological event—though recovery from a small myocardial infarction may result in this pattern, with retention of an atrial sound. We believe that an atrial sound associated with an enlarged "a" wave and a palpable atrial beat is nearly always pathological. When there are no diagnostic pointers to other forms of heart disease the most likely cause is early coronary heart disease[30] or healed myocardial infarction, a commonly undiagnosed condition.[31 32] In a recent follow up study of 19 patients with atrial sounds and enlarged atrial beats but no other evidence of heart disease we found that eight had evidence of coronary heart disease after 15 to 79 months (mean 36 months). The only one to come to autopsy had a healed infarct which had not been diagnosed in life. To determine the true significance of the "lone atrial gallop" it would be most useful to include apexcardiograms and phonocardiograms in long term population studies.

H. J. N. Bethell, M.B. M.R.C.P.
P. G. F. Nixon, M.B. F.R.C.P.
Cardiac Department
Charing Cross Hospital
Fulham Palace Rd.
London W 6 England

H. J. N. B. in receipt of a research fellowship from the Board of Governors of Charing Cross Hospital

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Diagnosis and treatment—past and present

The practice in clinical medicine today is to define the symptoms signs and other clinical data according to a well established diagnostic term and to institute therapy according to the prevailing practices of the day That is a good practice in most instances However there is also the practice among most doctors to define the clinical manifestations with the most likely diagnostic term known when the data do not fit fully and to treat accordingly This tendency is certainly erroneous for many apparent reasons Besides resulting in mismanagement most important is that the practice of fitting and forcing a diagnosis into an existing diagnostic pigeonhole fails to advance new concepts in medicine Had all physicians done this 100 years ago and had they continued to do so clinical medicine today would be where it was 100 years ago When clinical data definitely do not satisfy the criteria for any conventional diagnosis, further studies thoughts and ideas are mandatory A new syndrome disease or mechanism of disease may be present. Habits are most difficult to modify One s thinking and behavior should not be governed strictly by existing knowledge habits behavior motivation, efforts and indolence When the clinical data do not fit a diagnostic syndrome admit it and act accordingly This practice will lead to new developments and insure the patient s therapeutic welfare

George E. Burch, MD
Department of Medicine
Tulane University School of Medicine
1430 Tulane Ave
New Orleans La. 70112

Letters to the Editor

How dangerous is propranolol?

To the Editor

I have read the article entitled "Adverse reactions to propranolol in hospitalized medical patients A report from the Boston Collaborative Drug Surveillance Program" (David J Greenblatt and Jan Koch Weser Am Heart J 86 478 Oct 1973) with great interest There are however some points that I would like to stress because otherwise one might acquire the impression that propranolol is a far more dangerous drug than it really is when used according to commonly accepted precautions

The clinical data on the eight individuals with life threatening complications are too sparse to justify any firm conclusions However from the published data it seems to me that at least patients Nos 2 3 5 and 7 probably should not have been given propranolol There will always exist a great hazard when propranolol is given to an individual with heart failure (especially left ventricular failure) and/or acute coronary insufficiency Concerning patients Nos 1 4 6 and 8 it is difficult to draw any conclusions but before blaming the drug solely one would like to have access to detailed clinical data. The article is valuable in stressing that propranolol is a dangerous drug if ordered for patients with well known contraindications to its use (If there is a strong indication for the use of a beta blocker in such cases I think that practolol should be used as this beta blocker has been used successfully also in acute coronary emergency situations)

The article is also valuable in restressing that when severe cardiac symptoms occur during beta blocker therapy they occur rapidly i e mostly during the introduction of therapy and whether small or large dosages are used.

Jan Eriksen, Research Fellow M D
Med. Dept. B State University Hospital
Oslo Norway

Reply

To the Editor

In our study hospital physicians responsible for patients clinical care made decisions to administer propranolol and judged certain unwanted clinical events to be drug related adverse reactions It is difficult to say in retrospect whether or not such decisions and judgments were always correct We agree that the hazards of therapy with beta adrenergic antagonists are greater in patients with cardiac disease whose cardiac function is dependent upon adrenergic stimulation [1, 2] This probably applies to practolol as well as propranolol but we do not have sufficient data on practolol to assess its hazards since it is not available for clinical use in the United States.

David J Greenblatt M D
Jan Koch Weser M D
Massachusetts General Hospital
Boston, Mass. 02114

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George E Burch, MD
Department of Medicine
Tulane University School of Medicine
1430 Tulane Ave
New Orleans La. 70112

Books received

Fitness Health, and Work Capacity International Standards for Assessment Edited by Leonard A Larson, New York, 1974 Macmillan Publishing Company Inc 593 pp $14 95

Synopsis of Clinical Pulmonary Disease Edited by Roger S Mitchell, St Louis 1974 The C V Mosby Company 192 pp $7.50

How to Live With Your High Blood Pressure By William A Brams MD New York, 1973 Arco Publishing Company 145 pp $5 95

Coronary Heart Disease and the Mucopolysaccharides (Glycosaminoglycans) By Lester M Morrison, MD and O Arne Schjeide PhD Springfield Ill 1974 Charles C Thomas Publisher 251 pp $16 50

Book reviews

Hypertension Manual Edited by John H Laragh M D New York 1974 Dun Donnelley Publishing Corporation 934 pages

Laragh has edited a timely book of over 900 pages on hypertension With the present concern about the importance of hypertension as a serious problem in health this book with many contributors presents a fairly thorough review of hypertension The contributions include six parts related to epidemiology mechanisms methods management the renin system antihypertension agents and diet The reader will find this to be an extensive consideration of hypertension This is one disease that can be detected early and controlled so that its complications which are responsible for serious morbidity and many deaths can be overted. There is a need to know hypertension and its treatment extremely well Doctors and physiologists as well as students will welcome this important publication It is highly recommended.

Chirurgie Vascularie By Cl Olivier Paris 1973 Masson et Cie 268 pp 66 Fr

This small paperback book is limited to surgery on arteries veins and lymphatics. It is concerned with details in operative technique The illustrations are all excellent and diagrammatic There are no photographs of operative procedures or operative fields This book should be of special interest to surgeons in training who are developing techniques of vascular suturing vascular repair and bypassing operations The illustrations in themselves indicate Olivier s approach to vascular surgery This is an interesting book of a little over 250 pages limited to surgical technique and therefore is not concerned with diagnosis general aspects of management or pathogenesis of vascular disease

Stress and the Heart Edited by Robert S Eliot M D Mount Kisco N Y 1974 Futura Publishing Company 415 pages

Any cardiologist is aware of the importance of stress in cardiology Stress psychic and physical can precipitate congestive heart failure and angina pectoris as well as myocardial infarction Stress is used to study heart disease It is used to treat heart disease as well All physicians and patients are regularly concerned with stress in the management of heart disease Eliot and his numerous contributors present in many presentations a thorough review of the current status of the role of stress in the practice of cardiology It is convenient for the reader to find such an extensive discussion of stress in cardiology in a single book This is a fine book that should interest general practitioners, internists and cardiologists. The bibliographies included will be extremely useful to those interested in studying some of the original publications of observations of the influence of stress on the heart Unfortunately as is so common today the important older literature is neglected.

The Myocardium Failure and Infarction. Edited by Eugene Braunwald M D New York 1974 HP Publishing Co Inc 409 pages

Eugene Braunwald has edited an important publication. The myocardium does the work for the entire circulation. It must function well in order to maintain good health. Although a great deal remains to be learned about the myocardium much has been learned in recent years. With the assistance of many contributors Braunwald has produced a book for students and doctors of medicine a review of myocardial function and ischemic myocardial disease The presentations are grouped into seven sections The sections are concerned with mechanisms of cardiac contractions, mechanics of heart failure manifestations of heart failure treatment of heart failure etiology of myocardial infarction consequences of myocardial infarction. Unfortunately the references are not extensive. This is understandable for a book designed to condense for students and trainees the large subject of myocardial function and infarction The illustrations are good and the presentations are concise This will be welcomed by readers However those most responsible for the advancements in knowledge about the myocardium are not adequately revealed, but this is not a book on the history of research on the myocardium but an assessment of the present state of knowledge for those who have not followed the literature carefully or who wish to review the problem briefly and rapidly Readers will find this to be a valuable contribution to cardiology

American Heart Journal

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Editorial

Penicillin and the control of syphilis

E M C Dunlop MD FRCP
London, England

Just over 30 years ago (in June 1943) Mahoney Arnold, and Harris[1] used penicillin for the first time for the treatment of patients suffering from syphilis They treated four patients who had darkfield positive primary syphilis with good initial results Soon it became apparent that penicillin could be used as a brief nontoxic and highly effective treatment This was in marked contrast to preparations of arsenic and of bismuth which sometimes were even more toxic to the patient than to the spirochete these had to be given in prolonged courses lasting months to produce a cure so that many patients defaulted before they had received adequate treatment

Although penicillin was soon accepted as a highly effective agent for controlling the active manifestations of syphilis, it took longer for physicians to determine the eventual outcome for treated patients In a timely monograph Idsøe Guthe and Willcox[2] have reviewed and summarized the knowledge that has been gained during the past thirty years about the treatment of syphilis with penicillin

It was soon clear that *Treponema pallidum* was one of the most sensitive of all microorganisms to the action of penicillin A concentration of only 0 03 U per milliliter was shown to be fully treponemacidal and this sensitivity has apparently remained unchanged although strains of many other organisms that are initially resistant to penicillin or have become so have been discovered no such resistant strain of *T pallidum* has been demonstrated

Principals of treatment A treponemacidal level of penicillin (0 03 U per milliliter) should be maintained in the blood of the patient for an adequate time The division time of *T pallidum* (in early syphilis at least) is 30 to 33 hours[3,4] It seems that a treponemacidal level of penicillin should be maintained for some 7 to 10 days so as to cover a sufficient number of divisions to be effective Any intervals during which the level of penicillin is not treponemacidal should not be long enough to permit multiplication of the organism A continuously maintained low level is more effective and economical than high serum levels for brief periods separated by long intervals.

The dosage of penicillin required to cure syphilis increases with the number of treponemes present[5] thus when penicillin was administered to rabbits during the incubation stage after they had been infected with *T pallidum* the incubating disease could be aborted or cured with 1/32 of the dose required to cure the established disease[6]

In late syphilis the infection is relatively inactive hence although the number of treponemes in the infected person may be less than in secondary syphilis it may well be that the number of resting organisms that are accordingly insusceptible to penicillin is greater

As Moore[5] pointed out, treatment for syphilis

From the Whitech pel Cl ic The London Hosp tal, Moorfi lds Eye Hospital, nd the Instit te of Ophthalmology London England

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Diagnostic ultrasound in pediatrics

A comprehensive program on the value of diagnostic ultrasound as applied to pediatrics will be presented at The Johns Hopkins Hospital on September 5 6 1974 Both practical and theoretical considerations which apply specifically to the pediatric age group will be stressed. The faculty which has been selected for its contributions to the field of pediatric ultrasound includes Donald Brascho Richard Dallow John Dorst Barry Goldberg Walter Henry Daniel NcNulty Richard Meyer Daniel Pieroni David Sahn Roger C Sanders Sumio Uematsu Roberta Williams and others Fee for the course will be $150 ($100 for residents) Further details may be obtained from Roger C Sanders M D Department of Radiology The Johns Hopkins Hospital Baltimore Md. 21205

1975 Pediatric cardiology examination

The Sub Board of Pediatric Cardiology will offer its next written examination on May 2 1975 The registration period for this examination will extend from Oct. 1 1974 to Jan 1 1975 Application requests will be held on file until the opening of the registration period, at which time the necessary forms will be sent to those who have requested them Please direct correspondence to American Board of Pediatrics 3930 Chestnut St Philadelphia Pa 19104

Three days of cardiology

The American Heart Association Council on Clinical Cardiology in cooperation with the New York Heart Association will present an intensive three day program in cardiology at the Americana Hotel in New York City Sept 20 22 1974 Samuel Zoneraich M D F A C C will direct the course entitled Noninvasive methods in cardiology—1974 It will present an up to date and comprehensive review of basic concepts physiologic correlates and interpretations in a clinical setting related to phonocardiography echocardiography apexcardiography radarkymography phonoanteriography venous and arterial pulses systolic time intervals stress testing pacemaker clinical and radionuclide angiography For further information write to George E Stewart Jr American Heart Association 44 E 23rd St New York N Y 10010

Workshop on prostaglandins

A workshop on the prostaglandins in clinical medicine will be presented by The University of Texas Health Science Center at Houston Medical School Division of Continuing Education and Baylor College of Medicine on Sept 19 1974 at Houston Texas Developments both in scope and in depth concerning the prostaglandins are occurring rapidly Their roles in pregnancy and abortion are well documented. Their importance in the G I track and cardiovascular system is becoming recognized, as is their importance in platelet metabolism A workshop designed to review the recent developments of this exciting new agent has been arranged Five top U S Authorites will participate in the program as guest lecturers For further information write The Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education, P O Box 20367 Houston Texas 77025

Congress of International Rehabilitation Medicine Association

The second Congress of the International Rehabilitation Medicine Association will be held in Mexico City from Oct. 27 to Nov 1 1974 The subject matter of the Congress will include the newest methods of rehabilitation of persons with all sorts of handicaps disorders of the musculo skeletal nervous, cardiovascular or respiratory systems cancer problems of vision communication or alcoholism mental disorders and the need for special education There will be symposia plenary sessions, special interest sessions free papers, work groups, and instructional courses For further information please contact the General Secretary of the Congress, Dr Alfonso Tohen Apartado Postal 7 1427 Mexico D F Mexico

Workshop in electrocardiography

The Rogers Heart Foundation and St Anthony s Hospital announce the fourteenth Workshop in Electrocardiography to be held at the Tides Hotel and Bath Club Redington Beach Florida on October 10 through October 14 1974 The workshop directed at cardiac nurses and interested physicians will be hosted by Henry J L Marriott M D and the guest speaker will be J Graeme Sloman B Sc F R C P Director Cardiac Laboratory Royal Melbourne Hospital Melbourne Australia For further details regarding this workshop please write Rogers Heart Foundation St Anthony s Hospital St Petersburg Fla 33705 or telephone (813) 894 0790

lart Borel, and Durel[15] in a series of publications starting in 1962 and subsequently by other workers including Smith and his collaborators.[16] Some of these forms were artifacts,[17] some were detected in cases in which there was no definite evidence of treponemal infection but others were *T pallidum* as shown by the experimental infection of animals by a number of workers including Hardy and others[18] who recovered *T pallidum* from a baby who died after treatment of early congenital syphilis the organism was shown to be sensitive to penicillin and highly pathogenic to rabbits This was the first report of the recovery of undoubted *T pallidum* after the treatment of early syphilis The subject of persisting treponemes has been reviewed recently.[19 20 21] In most of the few cases in which animals have been successfully inoculated the organisms apparently had reduced virulence It is of course possible that ' persistent treponemes with reduced or even no virulence to rabbits might produce disease in the human host sensitized to their products It is of interest that lesions were precipitated in some inoculated rabbits by the administration of cortisone.[15 22] Unless the assumption is made that treatment always eradicates *T pallidum* it is reasonable to accept that the organism may sometimes be detected during follow up It is clear that tests for treponeme like forms are insensitive and time consuming research procedures in most cases the nature of such forms is uncertain and so is their significance to the patient.[21] The results of studies of persisting treponemes do not alter the conclusion that penicillin is clinically highly effective in controlling syphilis.

The Jarisch Herxheimer reaction Mahoney Arnold, and Harris[1] reported that each of their four patients treated for primary syphilis in 1943 developed malaise fever swelling of penile ulceration and of regional lymph nodes within the first eight hours of treatment

Such a Herxheimer reaction will occur when any antitreponemal agent is used in adequate dose in about 75 per cent or even more[23] of cases of early syphilis. It is unimportant clinically except that its frequent occurrence indicates that the patient must be warned what to expect so that he does not fear that the treatment is poisoning him

In late syphilis if vital structures (such as the coronary ostia, larynx or brain) are attacked by active syphilitic inflammation or in early congenital syphilis the Herxheimer reaction may be dangerous In such cases it is now customary to administer corticosteroids by mouth dosage suitable for an adult would be prednisolone 10 mg three times a day for three days starting 24 hours before the first dose of penicillin so that the corticosteroid is continued for the first 48 hours of treatment with penicillin Although it seems that this may obviate or minimize the Herxheimer reaction the matter has not been proved beyond doubt for late syphilis with a control series for obvious reasons

Studies reviewed by King[24] indicate that the Herxheimer reaction is an all or none phenomenon Thus it is not obviated or minimized by starting treatment with small doses of penicillin or of any other strongly treponemacidal agent

Allergy to penicillin. In 1969 6 6 per cent of patients who attended clinics for sexually transmitted diseases in the United States of America gave a history of allergy to penicillin.[25] In cases of allergy to penicillin that antibiotic is contraindicated and alternative treatment should be given (ideally by injection[8])

Cephaloridine has a more marked antitreponemal effect than the tetracyclines.[26] Intramuscular injections of G1 twice a day for ten days are effective treatment for uncomplicated early and late syphilis This course should be prolonged to a total of 15 to 17 days for complicated syphilis Because the cephalosporins contain a β lactam ring identical to that in the penicillin nucleus a few patients who are allergic to penicillin may also be allergic to cephaloridine For this reason cephaloridine (and other cephalosporins) are contraindicated in the cases of patients who have had anaphylactic reactions to penicillin

The following dosage schemes will produce results that are almost as good as from penicillin in patients suffering from early uncomplicated syphilis Careful follow up is particularly essential

Erythromycin three 250 mg tablets four times a day for ten days (30G) for uncomplicated syphilis much larger total doses have to be used for neurosyphilis and for the treatment of pregnant women this is because erythromycin diffuses less well into the spinal fluid and the fetal circulation than do the tetracyclines

Chlortetracycline and oxytetracycline three

should preferably be administered by injection because this eliminates many variable factors With treatment by mouth the patient may not take the remedy as ordered (and may even give half the tablets to a sexual partner whose existence has been concealed), if the patient does take the tablets as ordered absorption may be poor or variable If treatment has been given by injection it is known that effective blood levels will result because sufficient over dosage should be used (as in the schedules outlined below) to allow for the variation in serum level[9] that may result from the same dosages of the same preparation in the same or in different individuals

Dosage If aqueous benzyl penicillin G is used one intramuscular injection may produce a treponemacidal level lasting several hours The dosage of each injection and the number of injections in each 24 hour period should be sufficient to obviate long penicillin free periods Treatment should be continued for not less than 7 to 10 days for uncomplicated syphilis and for 14 to 17 days for complicated syphilis (iritis, neurosyphilis cardiovascular syphilis)

Procaine penicillin G may be given as 600 000 U by intramuscular injection once a day for 10 days for uncomplicated syphilis and for 14 to 17 days for complicated syphilis If an adequate preparation of procaine penicillin with 2 per cent aluminum monostearate (PAM) is used the absorption is more gradual so that injections do not have to be given daily If the injections are given daily and the patient defaults during treatment, the depot of PAM that the patient has received may result in cure

If benzathine penicillin G (DBED) is used, one injection of 2 4 mega units will produce a treponemacidal effect for up to three to four weeks In theory this dosage should be adequate and it appears to be so in most cases of primary syphilis Nevertheless, infection of relatively inaccessible sites such as the eye or cerebrospinal fluid must occur in a high percentage of cases of early syphilis Thus clinically manifest iritis was reported by Moore[10] in 4 5 per cent of cases of early secondary syphilis and 9 per cent of cases of relapsing secondary syphilis Benzathine penicillin in a dosage of 2 4 or 2 5 mega units resulted in a failure rate of 21 per cent in asymptomatic neurosyphilis compared with 10 5 per cent for other preparations of penicillin producing higher serum levels[11] Doubling the dose of benzathine penicillin halved this failure rate[3] Aqueous benzyl penicillin and particularly benzathine penicillin do not readily enter the eye[12] For these reasons if benzathine penicillin is used it is suggested that two injections each of 2 4 mega units separated by an interval of two weeks, should be given for uncomplicated syphilis and three such injections separated by similar intervals for complicated syphilis An added reason for using this higher dosage is that the follow up rate after treatment is often low[13]

Results of treatment

Early syphilis Healing of lesions was prompt In both seronegative primary syphilis and in secondary syphilis retreatment was required in only about 3 per cent of the cases reported by Jefferiss and Willcox[14], these authors considered that most of the retreated patients had been reinfected After successful treatment the titers of tests for reagin (WR CWR, VDRL Kahn, etc) progressively decline so that in general about 90 per cent of patients will be seronegative to such tests after one year

If penicillin had proved ineffective in the prevention of late manifestations of syphilis there would have been an increase in their incidence by now to follow the epidemic of early syphilis that was treated with penicillin in the post war era In fact there has been a marked decline in the incidence of late syphilis in those countries in which penicillin was widely used for the treatment of early syphilis at that time This is part of the great contribution to public health made by penicillin

Late syphilis In general, adequate treatment heals and prevents the progress of syphilitic inflammation so that the results of treatment are good

However treatment cannot restore irreversibly damaged tissue thus aortic incompetence may develop or worsen following treatment as a 'therapeutic paradox

Tests for reagin remain positive in most cases but the titer declines over the years after successful treatment The specific tests for antitreponemal antibody (TPI FTA ABS and TPHA) remain positive despite clinical cure of the infection this positivity is not an indication for retreatment

"Persisting treponemes.' The presence of treponeme like forms in patients following the treatment of syphilis was reported first by Col

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Venereology and the control of syphilis In the United Kingdom, the new speciality of venereology has developed to deal with sexually transmitted diseases and their related problems It became apparent that syphilis could not be managed adequately as an entity separate from the other sexually transmitted diseases Such separation is illogical because the presence of one such disease is an indication of possible exposure to the others Thus of 222 women found to have early infectious syphilis in London no less than 58 (26 per cent) attended because of symptoms that were entirely or partly due to other sexually transmitted diseases [29] Of 513 cases of trichomoniasis in women diagnosed in London, 155 (30 per cent) occurred in association with gonorrhea in 45 per cent of the cases trichomoniasis occurred in association with at least one other sexually transmitted infection thus 38 (8 5 per cent) out of 449 women with trichomoniasis had treponemal infection [30] Of 28 women who had given birth to babies suffering from ophthalmia neonatorum due to TRIC agent, ten had other sexually transmitted infections, including one patient who was treated for two attacks of early syphilis [31]

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' This came as a surprise to the many persons who for more than 10 years had believed that 'penicillin" was the magic word which would eradicate venereal disease Belief in this myth was so strong, in fact that it influenced an almost tragic de emphasis of the epidemiology of syphilis, from the classroom of the medical college to the office of the private physician to the department of public health

Almost too late, we were forced by circumstance to recognize the fact that it would take more than a 'miracle drug to control this disease and keep it controlled.

Venereology and the control of syphilis In the United Kingdom the new speciality of venereology has developed to deal with sexually transmitted diseases and their related problems It became apparent that syphilis could not be managed adequately as an entity separate from the other sexually transmitted diseases Such separation is illogical because the presence of one such disease is an indication of possible exposure to the others Thus, of 222 women found to have early infectious syphilis in London no less than 58 (26 per cent) attended because of symptoms that were entirely or partly due to other sexually transmitted diseases [29] Of 513 cases of trichomoniasis in women diagnosed in London, 155 (30 per cent) occurred in association with gonorrhea, in 45 per cent of the cases trichomoniasis occurred in association with at least one other sexually transmitted infection thus 38 (8 5 per cent) out of 449 women with trichomoniasis had treponemal infection [30] Of 28 women who had given birth to babies suffering from ophthalmia neonatorum due to TRIC agent, ten had other sexually transmitted infections, including one patient who was treated for two attacks of early syphilis [31]

Over the years venereology has established itself in the United Kingdom so that there are now over 200 clinics scattered throughout the country for the management of all the sexually transmitted diseases Skilled advice in this field treatment follow up and contact tracing is generally available to the community and this service is widely used Not only is it logical for one speciality to deal with all sexually transmitted diseases together rather than with artificially restricted sectors of this field but this unification creates an area of work that is more interesting for students doctors and nurses so that the recruitment of staff is aided It seems that the first step in establishing such a service must be taken in the medical schools All undergraduate medical students should be taught about these common diseases as was recommended by the National Commission on Venereal Diseases [32] This was regarded as the first step to combat the increasing incidence of disease in the United States of America[13] by an International Travelling Seminar organized by the World Health Organization and the International Union against the Venereal Disease and Treponematoses

In 1963 the only one of the ten undergraduate teaching hospitals of London University that did

not have a department for the care of sexually transmitted diseases fell into line with the others and established one From that time on all medical students in the United Kingdom have received clinical instruction in venereology from departments associated with their teaching hospitals. Clinics for the management of the sexually transmitted diseases have been established in most large general hospitals to complete the service that they give to the community Training posts in venereology are available for medical and nursing graduates particularly in university centers sometimes for doctors as part of a planned rotation of medical appointments Such postgraduate education is essential for the training of staff for the future After they have completed specialist training some physicians take part time posts in venereology that permit private practice which is thus of a higher standard in this field than that obtained in many other parts of the world.

The incidence of sexually transmitted disease in a community gives an indication of the effectivity of control measures

The United States of America has a population that is approximately four times greater than that of England and Wales In England and Wales in 1972 54 974 cases of gonorrhea and 1 695 cases of early syphilis (primary secondary and early latent) were reported[33,34] so multiplication of these figures by four will give approximately the number of cases that might have been expected in the United States of America if the rates of infection there had been the same as in the United Kingdom However the reported figures for the United States of America for the year 1972 were 718 401 cases of gonorrhea (instead of 220 000) and 44 354 cases of early syphilis (instead of 6 800) Moreover most patients treated for these diseases in the United Kingdom[36] attend clinics and appear in official statistics in the United States of America most do not. Thus estimates of the true incidence in the United States of America for 1972 were at least 2 5 million cases of gonorrhea and 85 000 new cases of primary and secondary syphilis[35] That eminently preventable disease early congenital syphilis was increasing in the United States of America[35] although vanishing in the United Kingdom[33,34]

It is probable that some of this difference in incidence is due to the establishment of venereology as a speciality in the United Kingdom It seems that this speciality will have an increasingly important part to play in the future in the care of the community this will include the control of syphilis

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Clinical communications

A contribution of intracavitary electrocardiography to the differential diagnosis of right ventricular diastolic restriction syndrome

Ivan G Maia
Cantidio Drumond Neto
Norival Romão
Marco Aurelio Santos
Jorge N Moll Filho
Munir Murad
Nelson Botelho Reis
Rio de Janeiro Brazil

The study of cardiopathies with ventricular diastolic restriction has been of specific interest to our group especially those which involve the right ventricle basically In a former communication we have discussed several clinical and hemodynamic aspects of these syndromes [1,2] Our first case of endomyocardial fibrosis was found in 1946 but not recognized until 1950 [1] In this study it is our purpose to introduce a further semiotic element which may be valuable in the differential diagnosis of various conditions which can develop involving significantly right ventricle compliance

The study was carried out by intracavitary electrocardiography a method widely employed in the study of activation of the heart in the diagnosis of complex arrhythmias in the diagnosis of certain congenital heart diseases such as the Ebstein anomaly and recently in recording the depolarization phenomenon of the His bundle and its ramifications. It is easily used in any hemodynamic laboratory because of its simple and innocuous technique

From the Centro de Investigações Cardiologicas e Se ta Enfermaria do Hospital Geral da Santa Casa do Rio de Janeiro Rio de Janeiro, B azil.

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Reprint requests Dr I an G Maia, Av N S d Copacabana n. 1394 pt. 502, Rio de Jan iro, Brazil ZC37

Material and methods

In all sixteen patients were studied (eleven were males and five were females) Their ages ranged from 11 to 44 with the average age being 22 Their diagnoses were made according to hemodynamic and routine clinical criteria The hemodynamic study included right and left heart catheterization determination of the cardiac output by dye dilution and angiograms selected according to each case The established diagnoses which served as controlling elements were as follows four patients with restrictive myocardiopathy four patients with constrictive pericarditis all confirmed surgically three patients with endomyocardial fibrosis having necroscopic confirmation in one case and five patients without right ventricle pathology We used the classic hemodynamic criterion for diagnosis of right ventricle diastolic restriction

After completing the hemodynamic and angiographic study we introduced a unipolar electrode catheter with platinum tip into the right ventricle The external terminal of the catheter was connected by a plug to the precordial V cable of a electrocardiogram channel of the registering set (Eletronics for Medicine) keeping the selecting lead switch in a V position In this way we obtained an endocavitary unipolar lead The catheter having a terminal hole registered the pressure of the cavity simultaneously testifying as to the localization of its termi

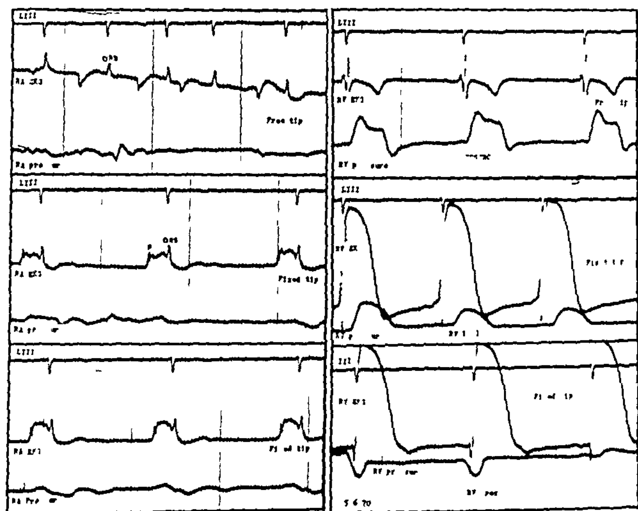


Fig 1 Normal patterns of monophasic action potential obtained in the right atrium and right ventricular cavity

nal Registering of the pressure was made by a Statham transducer (P23 AA) connected to the pressure channel of the registering set In a second electrocardiograph channel we monitored the patient with either Lead II or III

After verifying that the catheter was in right ventricle position we began working on it so as to insert its tip into the various parts of the inflow and outflow tract of the cavity searching for monophasic action potential in the intracavitary electrical register The endocavitary mapping was made in such a way that all possible regions of the cavity could be reached The dumping or disappearing of the simultaneous pressure register indicated that the tip of the catheter was contacting the ventricular endocardium Once the monophasic action potential was obtained the catheter was slowly removed from its position until fading of the action potential, with the prompt appearance of the pressure curve All these operations were done very carefully in order to avoid possible arrhythmias In Fig 1, one can see the type of monophasic action potential which was obtained when the tip of the catheter contacted the atrium or ventricular endocardium

Results

For a better sequence of results we shall divide the patients into several groups As we had fore seen in the group of the patients presenting no right ventricular pathology which served as controls we obtained large monophasic action potential when inserting the tip of the catheter into the various parts of the inflow and outflow tract of the right ventricle Momentary arrhythmias were often provoked when operating the catheter Fig 2 shows the curves obtained in this group There is a continual tracing A wide monophasic action potential was observed appearing on the endocavitary tracing with instant disappearance of the pressure curve whenever the tip of the catheter contacts the ventricular endocardium Operations with the catheter allow the appearance and disappearance of the action

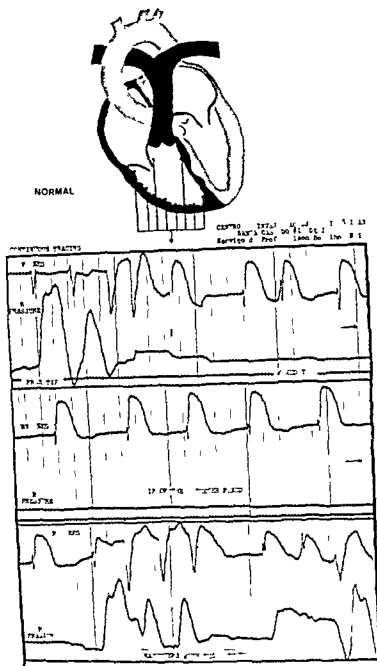


Fig 2. Normal group—wide monophasic action potential curves and arrhythmias obtained on the whole ventricular endocardic surface

potential and the pressure curve. The frequency with which these operations provoke arrhythmias were also observed. The upper drawing shows several parts of the ventricular endocardium which were explored. The behavior of this whole group was alike.

In the group of patients with myocardiopathy we obtained the same results as in the former normal group. Large monophasic action potentials were obtained in the outflow and inflow tract of the right ventricle. Fig. 3 represents an example of the group. One can observe the facility with which the arrhythmias are provoked when the catheter is used and the wide

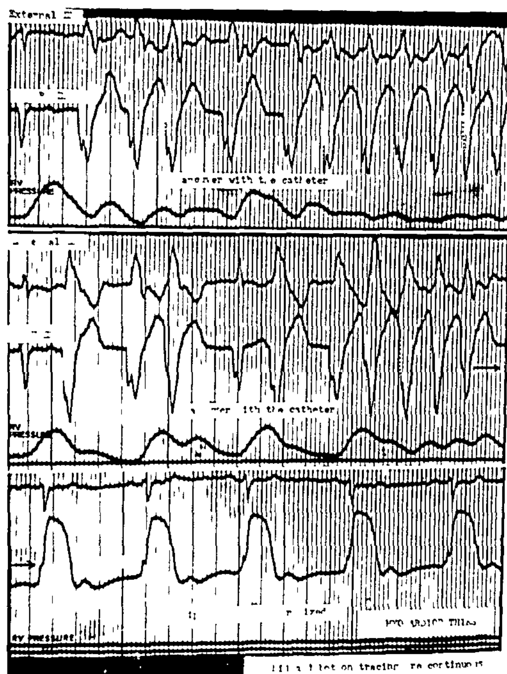


Fig 3 Group of patients with myocardiopathies—behavior identical to the normal group

curve of the monophasic action potential is obtained with the disappearance of the pressure curve The group having pericarditis showed the same behavior as the two former groups All four patients showed wide curves of the monophasic action potential and arrhythmias in all explored zones Fig 4 shows an example of the group In the upper chart we can see the various explored parts of the endocardium and the tracing shows gradual disappearance of the action potential when the tip of the catheter was slowly removed from its endocardial position The pressure curve testifies as to the position of the tip

The patients with endomyocardial fibrosis revealed a quite different behavior from the groups described above On no occasion were we able to provoke the appearance of a true monophasic action potential in the inflow tract and apex of the right ventricle this only happened at the outflow tract of the cavity In some places we only obtained a slight supra elevation of the J point not constituting, however the characteristic curve of the other groups The curve became characteristic only in the outflow zone of the cavity Arrhythmias were very rarely provoked when using the catheter in zones where there were no action potentials Figs 5 and 6 show an example of the group In Fig 5 we can

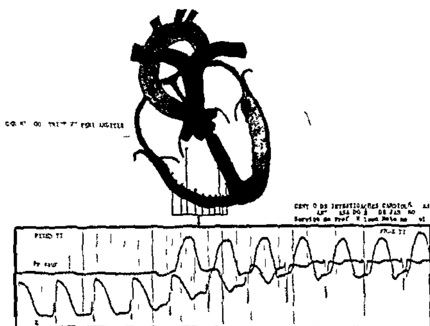


Fig 4. Group of patients with constrictive pericarditis—notice the immediate disappearance of monophasic action potential with simultaneous appearance of the pressure curve when the tip of the catheter loses contact with the endocardial surface

observe the various points of the ventricular endocardium which were explored. We can see that, in the outflow tract of the cavity there is a normal response i e the appearance of a large monophasic action potential in the intracavitary electrocardiogram The phenomenon is absent in the inflow tract and apex of the cavity Notice too a large presystolic wave in the ventricular pressure curve Fig 6 shows a slight elevation of the J point which disappears immediately when the catheter is removed from the endocardium This response however is not to be expected at all in such cases It is also observed that the pattern obtained inside the right ventricle was a QS pattern This occurred in more than one patient The third one showed an RS pattern A clear decrease in the QRS amplitude occurred, in this patient, when the catheter was driven into the endocardium of the cavity (Fig 7)

Discussion

The first works about intracavitary electrocardiography using an electrode catheter appeared in 1942 Since then we have learned that the pressure exerted by a platinum tip on the atrium and ventricular endocardium causes important local electrical modifications which culminate with the appearance of a wide monophasic action potential in the intracavitary electrocardiographic tracing (Fig 1) [10] This phenomenon does not represent a true transmembrane action potential since it is an extracellular event So far there is no final explanation for this finding but, doubtless its presence shows the existence of a wide endocardial electric activity meaning its integrity So the restrictive diseases which show a basic involvement of the myocardium and pericardium leaving an untouched endocardium must have an identical behavior as does a normal person This is true in the myocardiopathies and in constrictive pericarditis In endomyocardial fibrosis the essential lesion is the fibrosis [11,13] which reaches the endocardium and, very often the internal third of the myocardium Its localization is preferential In the right ventricle it involves basically the apex of the cavity causing its retraction and the inflow tract of the chamber It generally leaves a part of the septum and the outflow tract of the cavity which is abnormally dilated, intact The substitution of a healthy endocardium for fibrous tissue electrically inert, fully justifies our findings The exploration of several parts of the endocardium allow us to determine exactly those zones which

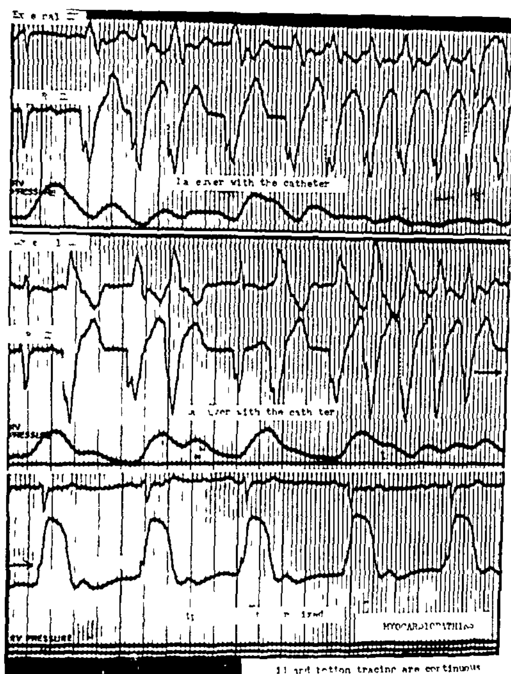


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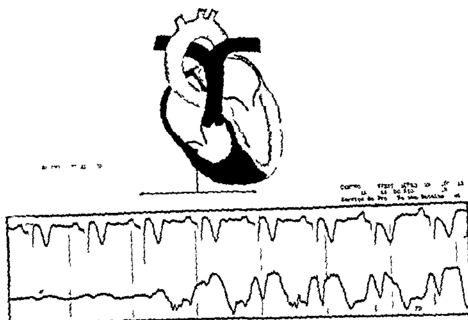


Fig 6 Group of patients with endomyocardial fibrosis—a slight endocardial response in the region near the tricuspid valve

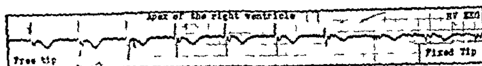


Fig 7 Group of patients with endomyocardial fibrosis—a clear decrease in the QRS amplitude without monophasic action potential occurred when the tip of the catheter was fixed at the apex of the right ventricle

otic sign of importance for the differential diagnosis of various entities that evolve involving significantly the right ventricular compliance

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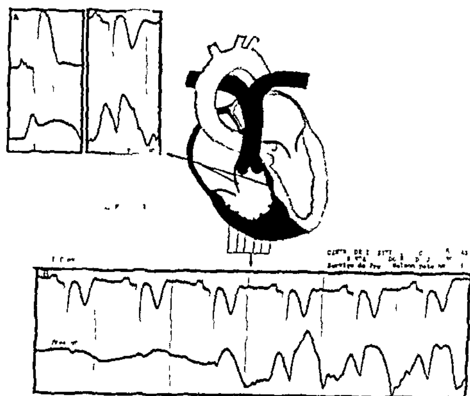


Fig 5 Group of patients with endomyocardial fibrosis. *A* outflow tract of the right ventricle showing a monophasic action potential *Left—fixed tip Right—free tip B, complete absence of the monophasic action potential in the inflow tract and apex of the right ventricle*

are still undamaged and also demonstrate that in spite of fibrosis there are still endocardial zones which are less damaged and still showing a small electrical response The appearance of arrhythmias when manipulating the catheter inside the ventricular cavity also indicates that *there is an electrical response from the* endocardium It is to be noted that in endomyocardial fibrosis they do not appear The behavior of the three patients in the group was identical In the first phases of the disease when the endocardium is not totally substituted by fibrosis a normal response could be found but when the disease is well established we believe that the electrical behavior of the endocardium is homogeneous with the whole group of endomyocardial fibroses A fair explanation has not yet been found for the QS pattern obtained in the right ventricular cavity and also *for the decreasing electric potential* formerly described It seems that the method should be used in the study of the other types of endocardial fibrosis

Summary and conclusion

The authors using an intracavitary electrocar*diographic technique* present a study of the endocardial electrical behavior of 11 patients *having right ventricular* diastolic restriction diagnosed by clinical and *hemodynamic criteria* and five patients not suffering from any disease in that cavity who served as a normal group for control purposes In the pathologic group there were four patients with myocardiopathies four patients with constrictive pericarditis and three patients with endomyocardial fibrosis The patients having myocardiopathy and constrictive pericarditis reacted like the normal group that is they showed large curves of monophasic action *potential in the intracavitary* electrocardiogram which were obtained in the endocar*dium of the inflow apex and outflow tract* of the *cavity whenever the tip of the platinum catheter* was inserted into these various places In endomyocardial fibrosis this sign is not shown at the apex and at the inflow tract of *the cavity only at the outflow tract of the chamber* The discovery of a silent endocardium is attributed to the fibrosis a basic anatopathologic element of this entity with a characteristic distribution They also call attention to the difficulty of starting *arrhythmias when handling the tip* of the catheter a reaction which is different from other groups with ventricular diastolic restriction They conclude that this finding is a further semi

Table I Clinical data in patients with direct posterior myocardial infarction

Patient	History of hospitalization for infarction	Diaphragmatic infarction ECG	Diaphragmatic infarction VCG	Ventriculogram diaphragmatic aneurysm	Aorto coronary bypass	Right	L Circ	LAD	Coronary dominance
1	+	+	+	+	+	100% Prox.	Mid 70%	75% Prox.	R
2	+	0	0	0	+	100% Post. Desc	75% Prox	100% Prox	R
3	+	+	+	+	−	−	100% Prox. (Dominant)	90% Prox.	L
4	+	0	0	+	+‡	100% Post. Desc	−	90% Prox	R
5	+	+	+	+	+	100% Prox	−	50% Prox	R
6	+	+	+	H†	+	100% Prox.	−	−	R
7	+	0	0	0	−	100% Prox.	100% Prox.	75% Prox	R
8	0	0	0	0	−	100% Prox.	95% Prox.	90% Mid	R
9	NA	0	+	H†	−	100% Prox	60% Prox	100% Prox	R

Not available
†Hypokinesis
‡Posterior infarction visualized at surgery

Table II Percentage of patients who satisfied various horizontal plane vectorcardiographic criteria of direct posterior infarction*

	Posterior infarction (%)	Normal subjects with anterior loops (%)
40 msec > 0	88 (8 of 9)	85 (11 of 13)
40 msec ≥ 16	67 (6 of 9)	54 (7 of 13)
60 msec > 0	0 (0 of 9)	1 (1 of 13)
Max. QRS ≥ −3	100 (9 of 9)	92 (12 of 13)
Half area vector > 0	67 (6 of 9)	69 (9 of 13)
Half area vector ≥ 10	56 (5 of 9)	46 (6 of 13)
Two-thirds QRS area anterior	56 (5 of 9)	46 (6 of 13)
Anterior voltage ≥ 0.5 mV	45 (4 of 9)	31 (4 of 13)
Anterior voltage ≥ 0.6 mV	45 (4 of 9)	31 (4 of 13)
Anterior accession time ≥ 30 msec	78 (7 of 9)	38 (5 of 13)
Anterior duration ≥ 42 msec	67 (6 of 9)	69 (9 of 13)
Anterior duration ≥ 50 msec	33 (3 of 9)	31 (4 of 13)
Anterior/posterior QRS voltage ratio > 1	45 (4 of 9)	38 (5 of 13)
Anterior displacement of afferent loop	100 (9 of 9)	77 (10 of 13)
Counterclockwise QRS rotation	100 (9 of 9)	100 (13 of 13)

*None of the groups differ significantly (Chi square)

hospitalization for an acute myocardial infarction (This history was not available in one patient.) The electrocardiogram did not show a direct posterior infarction ($RV_1/SV_1 > 1$ RV_1 and/or $RV_2 \geq 0.04$ sec.) in any of these patients.[5] The electrocardiogram was compatible with a diaphragmatic infarction in four patients (Leads Q III and $aV_F \geq 0.04$ sec and Q ≥ 25 per cent of amplitude of R)[6] The vectorcardiogram was indicative of a diaphragmatic infarction in five patients[7] The ventriculogram (right anterior oblique projection) showed dyskinesis of the diaphragmatic surface in four patients and hypokinesis in two patients The surgical reports were available in four of five patients who underwent a saphenous vein bypass. A posterior surface infarction was described in one of these patients (Table I)

The vectorcardiograms in these nine patients with a direct posterior myocardial infarction were compared to anteriorly oriented vectorcardiograms found to occur in 13 patients with no evidence of coronary heart disease Five of these patients were derived from a group of 25 healthy male volunteer subjects (medical students house staff or policemen) Eight additional anteriorly oriented vectorcardiograms were found in patients who underwent diagnostic coronary arteriography (usually for anginal like pain) and who were found to have normal coronary arteriograms of good quality To be included in this group of normal patients, it was required, in addition to normal coronary arteriograms that the patients had a normal resting electrocardiogram, no vectorcardiographic abnormality (with the possible exception of anterior displacement of the QRS loop) no history of a myocardial infarction

The anteriorly oriented horizontal vector loop The problem of distinction between direct posterior myocardial infarction and normal variation

Dinh Ha, M D
David I Kraft, M D
Paul D Stein, M D
Oklahoma City Okla

Vectorcardiograms of patients with a direct posterior myocardial infarction show diagnostic criteria which, in general distinguish such patients from most normal individuals[1-3] or from individuals with right ventricular hypertrophy[4] The criteria established for the diagnosis of a direct posterior infarction by vectorcardiography give emphasis to the horizontal plane 40 msec and 60 msec vectors the maximum QRS vector the half area vector, anterior voltage, anterior duration, and anterior accession time[1-3] When various combinations of the magnitudes and directions of these instantaneous vectors are significantly anterior, the diagnostic criteria for a direct posterior infarction are satisfied Such criteria appropriately describe the vectorcardiogram of patients with posterior infarctions However, a significant number of normal subjects also have anteriorly oriented vector loops which may present a difficult problem of differential diagnosis Only rarely is a previous vectorcardiogram available for purposes of aiding the differentiation The purpose of this study was to determine if the vectorcardiogram of patients with a direct posterior myocardial infarction can be distinguished from an anteriorly oriented QRS loop that occurs in normal individuals

From the Department of Medicine University of Oklahoma College of Medicine and Veterans Administration Hospital Oklahoma City

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Reprint requests to Dr Paul D Stein Veterans Administration Hospital 921 N E 13 St. Oklahoma City Okla 73104

Methods

Vectorcardiograms were reviewed in 490 patients who underwent diagnostic cardiac catheterization From this group 131 patients had an anteriorly oriented QRS loop in the horizontal plane An anterior loop was defined as one in which the maximum QRS vector was located anterior to the 0 to 180 degree line or one in which the half area vector was located anteriorly Forty of these patients were found to have anterior QRS loops associated with arteriographically determined coronary heart disease From this group of 40 patients those with complete occlusion of either the dominant right coronary artery, its posterior descending branch or the dominant left circumflex coronary artery were culled. There were nine such patients all were males (Table I)

Patients with anterior QRS loops who had possible right ventricular hypertrophy based upon the history physical examination chest roentgenogram electrocardiogram or a measured pulmonary arterial peak pressure of 40 mm Hg were eliminated from the study Patients with intraventricular conduction defects including Wolff Parkinson White syndrome were eliminated as were patients with cardiovascular abnormalities other than coronary heart disease such as aortic stenosis systemic hypertension or coarctation of the aorta

Diagnostic features of the histories, electrocardiograms vectorcardiograms ventriculograms and coronary arteriograms of the nine patients with posterior infarctions are outlined in Table I Seven patients gave a history of a previous

Table I Clinical data in patients with direct posterior myocardial infarction

Patient	History of hospitalization for infarction	Diaphragmatic infarction ECG	Diaphragmatic infarction VCG	Ventriculogram diaphragmatic aneurysm	Aorto coronary bypass	Right	L. Circ	LAD	Coronary dominance
1	+	+	+	+	+	100% Prox	Mid 70%	75% Prox	R
2	+	0	0	0	+	100% Post. Desc	75% Prox	100% Prox	R
3	+	+	+	+	−	−	100% Prox (Dominant)	90% Prox	L
4	+	0	0	+	+‡	100% Post. Desc	−	90% Prox	R
5	+	+	+	+	+	100% Prox	−	50% Prox	R
6	+	+	+	H†	+	100% Prox	−	−	R
7	+	0	0	0	−	100% Prox	100% Prox	75% Prox	R
8	0	0	0	0	−	100% Prox	95% Prox	90% Mid	R
9	NA	0	+	H†	−	100% Prox	60% Prox	100% Prox	R

NA Not available
†Hypokinesis
‡Posterior infarction visualized at surgery

Table II Percentage of patients who satisfied various horizontal plane vectorcardiographic criteria of direct posterior infarction*

	Posterior infarction (%)	Normal subjects with anterior loops (%)
40 msec > 0	88 (8 of 9)	85 (11 of 13)
40 msec ≥ 16	67 (6 of 9)	54 (7 of 13)
60 msec > 0	0 (0 of 9)	1 (1 of 13)
Max QRS ≥ −3	100 (9 of 9)	92 (12 of 13)
Half area vector > 0	67 (6 of 9)	69 (9 of 13)
Half area vector ≥ 10	56 (5 of 9)	46 (6 of 13)
Two-thirds QRS area anterior	56 (5 of 9)	46 (6 of 13)
Anterior voltage ≥ 0 5 mV	45 (4 of 9)	31 (4 of 13)
Anterior voltage ≥ 0 6 mV	45 (4 of 9)	31 (4 of 13)
Anterior accession time ≥ 30 msec	78 (7 of 9)	38 (5 of 13)
Anterior duration ≥ 42 msec	67 (6 of 9)	69 (9 of 13)
Anterior duration ≥ 50 msec	33 (3 of 9)	31 (4 of 13)
Anterior/posterior QRS voltage ratio > 1	45 (4 of 9)	38 (5 of 13)
Anterior displacement of afferent loop	100 (9 of 9)	77 (10 of 13)
Counterclockwise QRS rotation	100 (9 of 9)	100 (13 of 13)

*None of the groups differ significantly (Chi square)

hospitalization for an acute myocardial infarction (This history was not available in one patient.) The electrocardiogram did not show a direct posterior infarction ($RV_1/SV_1 > 1$ RV_1 and/or $RV_1 \geq 0.04$ sec.) in any of these patients[6] The electrocardiogram was compatible with a diaphragmatic infarction in four patients (Leads Q III and $aV_F \geq 0.04$ sec and Q ≥ 25 per cent of amplitude of R)[6] The vectorcardiogram was indicative of a diaphragmatic infarction in five patients[7] The ventriculogram (right anterior oblique projection) showed dyskinesis of the diaphragmatic surface in four patients and hypokinesis in two patients. The surgical reports were available in four of five patients who underwent a saphenous vein bypass. A posterior surface infarction was described in one of these patients (Table I)

The vectorcardiograms in these nine patients with a direct posterior myocardial infarction were compared to anteriorly oriented vectorcardiograms found to occur in 13 patients with no evidence of coronary heart disease Five of these patients were derived from a group of 25 healthy male volunteer subjects (medical students house staff or policemen) Eight additional anteriorly oriented vectorcardiograms were found in patients who underwent diagnostic coronary arteriography (usually for anginal like pain) and who were found to have normal coronary arteriograms of good quality To be included in this group of normal patients, it was required, in addition to normal coronary arteriograms that the patients had a normal resting electrocardiogram, no vectorcardiographic abnormality (with the possible exception of anterior displacement of the QRS loop) no history of a myocardial infarction

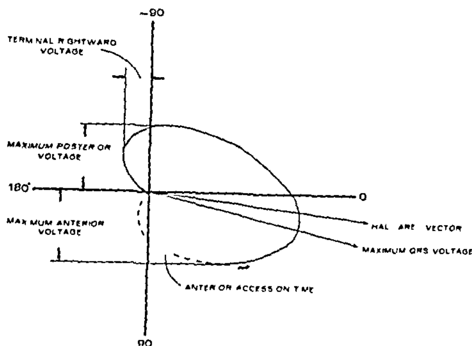


Fig 1 Diagram of anteriorly oriented horizontal plane QRS loop showing maximum QRS vector half area vector maximum anterior voltage maximum posterior voltage terminal rightward voltage and anterior accession time

no known previous abnormal electrocardiogram and a normal exercise test (if one was performed) None of these patients had a history, physical examination, roentgenogram or electrocardiogram suggestive of right ventricular enlargement The peak pulmonary arterial pressure was measured in five of these patients and found to be 32 mm Hg or less The ages of the 13 patients thought to have no evidence of heart disease were 41 ± 3 years (mean ± S E) The ages of those with coronary heart disease were 48 ± 3 years One normal patient was female, all other patients in the study were males

Twelve lead electrocardiograms were obtained the same day that the vectorcardiograms were performed This was usually one or two days prior to cardiac catheterization Vectorcardiograms were obtained by utilization of a Sanborn (Waltham, Mass) 1507A vector programmer and photographed with a Polaroid camera (Cambridge, Mass) The Frank system[8] was employed utilizing the fifth intercostal space Recordings were made at standardizations of 0 5 mV equal 2 cm, and 0 5 mV equal 5 cm Time dashes were set at 2 5 msec

Selective coronary arteriograms were performed on 35 mm cine at 64 frames per second Only studies of good quality were included. Each patient underwent selective injections of the coronary arteries performed in both the right anterior oblique and left anterior oblique positions Cine ventriculograms were performed during the power injection of 40 cm^3 of 75 per cent sodium and meglumine diatrizoate (Hypaque 75) into the left ventricle with the patient in the right anterior oblique position Left and right sided pressures were measured prior to the injection of any contrast material Right ventricular pressure was measured in five of the eight normal patients who underwent cardiac catheterization, and in five of nine patients with a direct posterior myocardial infarction Peak pulmonary arterial pressure was 32 mm Hg or less in the normal patients, and 36 mm Hg or less in patients with a direct posterior infarction

Methods of analysis

The direction and magnitude of the 20, 30, 40 50, and 60 msec vectors the half area vector and the maximum QRS vector were analyzed in the horizontal plane The magnitude of the right terminal vector, the maximum anterior vector, the maximum posterior vector, the anterior accession time the direction of rotation of the QRS loop and the T loop as well as the angle of the T loop, were also analyzed In the frontal and right sagittal plane the 40 msec vector the half area vector, the maximum QRS vector and the direction of rotation of the QRS loops and T loops were analyzed

The half area vector was obtained by a line

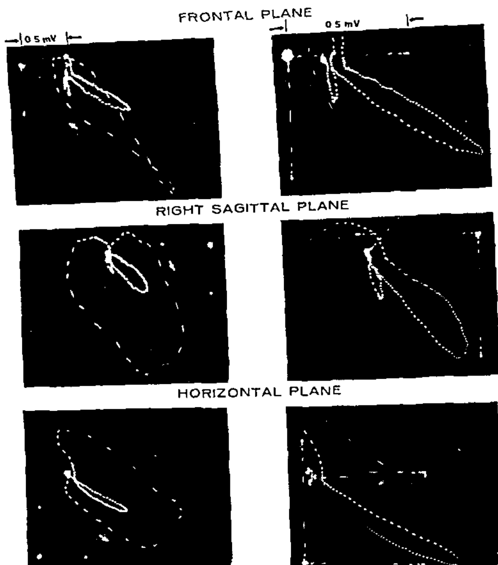


Fig 2 Vectorcardiogram of a 51 year-old man (Patient No 4) with complete occlusion of posterior descending coronary artery and posterior surface infarction visualized at surgery In the horizontal plane the 40 msec vector is 22° and the maximum QRS vector is 19 The half area vector is at 0 Maximum anterior forces are 0 45 mV The *anterior accession* time is 35 msec and the anterior duration is over 42 msec The vectorcardiogram satisfies the criteria for a posterior infarction utilized by some[2] but fails to meet the criteria utilized by others[1 9 10]

bisecting the QRS loop (Fig 1) The line was drawn by visual inspection of the loop and the accuracy was confirmed by ensuring equal numbers of squares on both sides of this line[4] By counting squares, the position of two thirds of the area of the loop was also determined. The terminal rightward voltage was determined as the rightward voltage of the terminal segment as projected upon the zero to 180 axis (Fig 1)[4] The maximum anterior voltage was determined as the maximum voltage projected anteriorly on the 90 to 270 axis[4] The maximum posterior voltage was determined as the maximum voltage projected posteriorly on the same axis[4] The anterior accession time was determined as the amount of time from the onset of the QRS loop to the maximum anterior vector The position of the afferent limb was determined by inspection

The criteria utilized for the vectorcardiographic diagnosis of a direct posterior myocardial

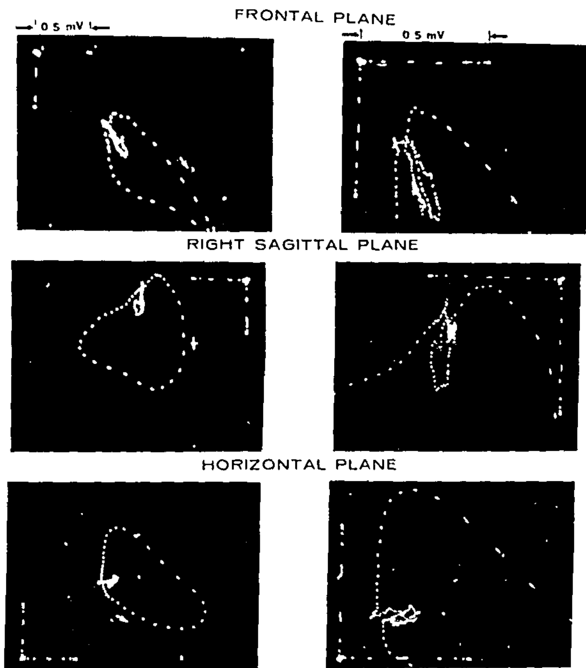


Fig 3 Vectorcardiogram of a 24 year old medical student In the horizontal plane the 40 msec vector is 23 and the maximum QRS vector and half area vector are 22 Maximum anterior forces are 0 88 mV The anterior accesion time is 32 msec and the anterior duration is over 42 msec This vectorcardiogram satisfies the diagnostic criteria for a posterior infarction suggested by several investigators [1,2,9,10]

infarction were those described by several previous investigators [1,3,9,10] Each of the suggested criteria was examined Specifically as proposed by Hoffman and associates,[1] a maximum anterior voltage of 0 5 mV or more, an anterior accession time of 30 msec or more, a half area vector of 10 degrees or more anterior to the O° horizontal plane axis and a total anterior duration of 42 msec were utilized as the four criteria which together, gave few (2 8 per cent) false positives The angle of the 40 msec vector (≥ 16° and maximum QRS (≥ −3°) were observed as suggested by Hugenholtz, Forkner and Levine [2] The criteria indicated by Chou and Helm[3] of two thirds of the entire loop anterior the half area vector anterior to 10°, the 40 msec vector anterior to 16° and the 60 msec vector anterior were examined. An anterior duration of 50 msec an anterior voltage of 0 6 mV or more and anterior displacement of the afferent loop were also suggested as possible criteria by Chou and Helm [3] although as they indicated these stringent criteria may

result in false negatives Others have utilized various combinations of these criteria For example Gray and associates[10] utilized the criteria of an anteriorly oriented 40 msec and half area vector McConahay and associates[9] utilized the following combination of criteria derived from the work of others a maximum anterior QRS voltage of 0 5 mV or more, an accession time of maximal anterior QRS forces of 30 msec or more an anterior to posterior QRS voltage ratio greater than one total anterior duration of 42 msec or more and anterior displacement of the afferent limb

Results

Comparable numbers of both groups of patients satisfied the various vectorcardiographic criteria for a direct posterior infarction with no statistically significant difference observed between the two groups (Chi square) (Table II) Sixty seven per cent (6 of 9) of the patients with a posterior infarction satisfied the dual criteria of the 40 msec vector $\geqq 16°$ and the maximum QRS $\geqq -3$ [2] or both the 40 msec and the half area vectors anterior [10] A comparable number of the normal subjects satisfied these combinations of criteria their number being 46 per cent (6 of 13) and 54 per cent (7 of 13) respectively Twenty two per cent of patients (2 of 9) with an infarction satisfied all of the criteria of Hoffman and associates[1] whereas 15 per cent (2 of 13) of normal subjects satisfied the same criteria (anterior voltage $\geqq 0$ 5mV anterior accession time $\geqq 30$ msec half area vector $\geqq 10°$ and anterior duration $\geqq 42$ msec.) There was no significant difference between these two groups Only one of the patients with an infarction and one of the normal subjects satisfied all of the criteria utilized by McConahay and associates[9] Illustrative examples of a vectorcardiogram in a patient with a direct posterior myocardial infarction (Fig 2) and a vectorcardiogram from a normal patient with an anterior horizontal QRS loop (Fig 3) are shown

There was no significant difference observed between any of the parameters measured on the vectorcardiograms of patients with a direct posterior myocardial infarction and the anteriorly oriented vectorcardiograms that occurred in normal individuals (t test) These results are clearly shown in Tables III and IV and in Fig 4 Specifically in the horizontal plane the

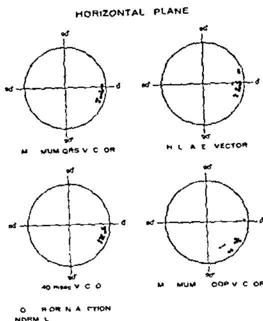


Fig 4 Location in horizontal plane of maximum QRS vector half area vector 40 msec vector and maximum T loop vector There were 13 normal subjects (squares) and nine patients with a posterior infarction (dots)

magnitude and duration of the 20 msec 30 msec 40 msec 50 msec 60 msec and half area vectors were similar

The right terminal voltage maximum anterior voltage maximum posterior voltage and ratio of the maximum anterior voltage to the maximum posterior voltage were similar in patients with a direct posterior infarction and normal individuals with anterior horizontal loops The anterior accession time was also similar in both groups The QRS loop in the horizontal plant rotated in a counterclockwise direction in each of the patients with a direct posterior infarction and in each of the normal patients The maximum T loop vector was at a comparable angle in patients with a direct posterior infarction (38 ± 10 degrees) and in normal subjects with anterior horizontal QRS loops (30 ± 4 degrees) (Table III Fig 4) Rotation of the T loop was similar in both groups (Table III) At first glance it would seem that the angle of the maximum QRS vector (25 ± 4 degrees) tended to differ from that of normal individuals (5 ± 11 degrees) even though the difference was not statistically significant. However as shown in Fig 4 the angle of the maximum QRS vector was similar in all but one of the patients In the group of normal sub-

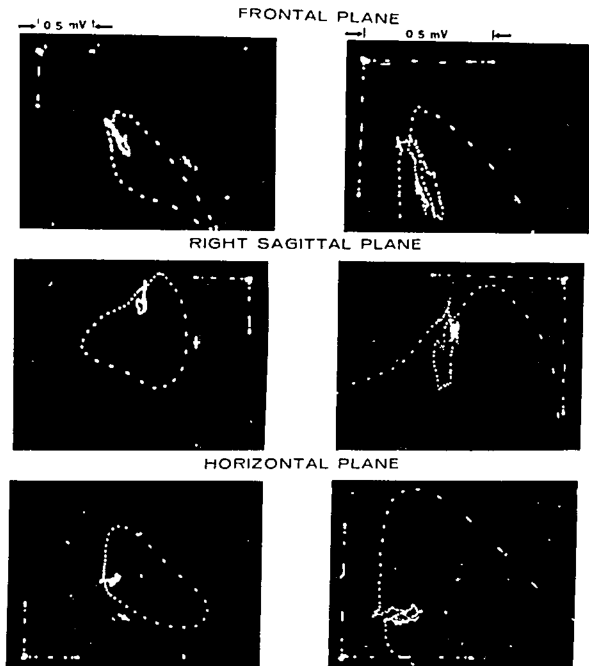


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Table IV A Frontal plane

	Direct posterior infarction		*Normal subjects with anterior loops*	
	Direction (degrees)	*Magnitude (mV)*	*Direction (degrees)*	*Magnitude (mV)*
40 msec vector	33 ± 4	1 2 ± 0 1	35 ± 5	1 3 ± 0 1
Half area vector	37 ± 6	–	38 ± 6	–
Maximum QRS vector	32 ± 6	1 5 ± 0 1	38 ± 3	1 5 ± 0 1
QRS loop rotation	8 of 9 CW 1 of 9 CCW		8 of 13 CW 5 of 13 Fig of 8	

Table IV B Right sagittal plane

	Direct posterior infarction		*Normal subjects with anterior loops*	
	Direction (degrees)	*Magnitude (mV)*	*Direction (degrees)*	*Magnitude (mV)*
Half area vector	82 ± 8	–	89 ± 6	–
Maximum QRS vector	86 ± 8	0 96 ± 0 07	84 ± 6	0 93 ± 0 08
QRS loop rotation	8 of 9 CW 1 of 9 Fig of 8		12 of 13 CW 1 of 13 Fig of 8	

dial infarction is of importance All of the patients included in this category had coronary heart disease with complete occlusion of the dominant right coronary artery or its posterior descending branch (eight patients) or complete occlusion of a dominant left circumflex coronary artery (one patient) (Table I) The posterior descending coronary artery whether it arises from the left circumflex or the right coronary artery courses down the posterior interventricular sulcus[12] Arteries which regularly contribute some portion of the blood supply to the posterior half of the left ventricle are the right coronary artery the left circumflex artery and the terminal portion of the left anterior descending artery[12] Mo t commonly the area of the posterior surface of the left ventricle supplied by the right coronary artery is the half near the posterior interventricular sulcus[12] One patient was shown on the operating table to have a visible area of infarction involving the posterior surface of the heart (Table I) Although none of these patients showed a direct posterior infarction on the electrocardiogram, the widely utilized electrocardiographic criteria for posterior infarction of an R/S ratio in Leads V_4R and V_1 greater than one is not infrequently absent in patients in whom the diagnosis is shown by other means[13] The vectorcardiograms in six of nine of these patients satisfied the criteria for a direct posterior infarction utilized by Hugenholtz Forkner and Levine[2] and Gray and associates[10]

Five of the 13 normal patients with anterior QRS loops were obtained from a group of healthy volunteer subjects In the remaining group of individuals who showed anterior QRS loops great care was taken to exclude the presence of coronary heart disease by any objective tests One cannot exclude the possibility of the rare occurrence of a myocardial infarction in individuals with normal appearing coronary arteries[14] It is emphasized, however, that such an occurrence is extremely rare Right ventricular hypertrophy was also excluded by all available objective tests including plane roentgenograms physical examination and electrocardiograms

The frontal plane vectorcardiogram may be of ancillary benefit in distinguishing patients with a direct posterior infarction from normal subjects with anterior QRS loops If vectorcardiographic abnormalities of a diaphragmatic surface myocardial infarction occur one might infer that

Table III Horizontal plane

	Direct posterior infarction		Normal subjects with anterior loops	
	Direction (degrees)	Magnitude (mV)	Direction (degrees)	Magnitude (mV)
20 msec	61 ± 6	0 37 ± 0 06	76 ± 10	0 33 ± 0 05
30 msec	41 ± 3	0 69 ± 0 07	44 ± 7	0 70 ± 0 07
40 msec	24 ± 3	0 94 ± 0 07	9 ± 7	0 90 ± 0 14
50 msec	-35 ± 19	0 67 ± 0 13	-33 ± 14	0 86 ± 0 14
60 msec	-91 ± 8	0 60 ± 0 08	-82 ± 13	0 53 ± 0 07
Half area	10 ± 5	—	8 ± 4	—
Maximum QRS	25 ± 4	1 1 ± 0 07	5 ± 11†	1 2 ± 0 10
Right terminal voltage	—	0 17 ± 0 04	—	0 21 ± 0 05
Maximum anterior voltage	—	0 57 ± 0 07	—	0 49 ± 0 05
Maximum posterior voltage	—	0 61 ± 0 07	—	1 1 ± 0 30
Maximum anterior voltage/ maximum posterior voltage ratio	—	1 0 ± 0 11	—	1 1 ± 0 30
Maximum T vector	38 ± 10	—	30 ± 4	—
Anterior accession time	30 ± 2 msec			30 ± 2
QRS loop rotation	CCW‡ 9 of 9			CCW 13 of 13
T loop rotation	CCW 8 of 9			CCW 11 of 13
	Fig of 8 1 of 9			Fig of 8 2 of 13

Mean ± standard error
†One patient had an anterior half area vector but a markedly posterior maximum vector causing this relatively low average value (see Fig 4)
‡CCW = counterclockwise

jects the average angle of the maximum QRS vectors was reduced due to a markedly posterior maximum QRS vector that occurred in one patient who had an anterior half area vector The magnitude of the maximum QRS vectors in patients with a direct posterior infarction (1 1 ± 0 1 mV) and in normal patients (1 2 ± 0 1 mV) was similar

In the right sagittal plane (Table IV), the direction of the half area vector, the direction of the maximum QRS vector, and the magnitude of the maximum QRS vector were similar in patients with a direct posterior infarction and in normal individuals with anterior loops

In the frontal plane five of nine patients with a posterior infarction had vectorcardiographic evidence[7] of an inferior infarction (Table I) None of the normal subjects had initial superior forces of sufficient magnitude to be compatible with a diaphragmatic infarction, since by definition, the occurrence of such a vectorcardiogram would have caused the patient to be excluded from the group of normal subjects The magnitude and direction of the 40 msec vector, and maximum QRS vector as well as the direction of the half area vector were similar in patients with a direct posterior infarction and in normal individuals with anterior loops (Table IV)

Discussion

Anteriorly oriented QRS loops are not uncommon in normal subjects In 70 normal patients reported by Hoffman and associates[1] the maximum QRS vector was between 0° and 60° in 41 per cent and between 10° and 60° in 24 per cent In a series of 60 normal subjects reported by Forkner, Hugenholtz and Levine[11] it was anterior in 22 per cent. Our own observations confirm the relative frequency of anterior QRS loops which occurred in twenty per cent (5 of 25) of healthy volunteer subjects It is not sufficient therefore to differentiate the vectorcardiogram of a posterior infarction from the usual vectorcardiogram that occurs in normal individuals The work of previous investigators clearly accomplishes this differentiation[1,3] The important problem is to distinguish the vectorcardiogram of a direct posterior infarction from that of the significant group of normal patients with anterior loops

The selection of the patients in this study who were thought to have a direct posterior myocar

Tricuspid atresia with l-transposition

Rajendra Tandon M D
José Marin Garcia M D
James H Moller M D
Jesse E Edwards M D
Minneapolis and St. Paul, Minn.

Inverted or l transposition is characterized by an abnormal relationship between the great vessels in which the aortic origin lies more anterior than and to the left of the pulmonary arterial origin The ascending aorta tends to sweep to the left of the pulmonary trunk

Two types of ventricular structure have been described in association with l transposition namely ventricular inversion (bulboventricular inversion) or isolated bulbar inversion In the majority of cases bulboventricular inversion is present that is the anatomic right ventricle lies on the left side and the anatomic left ventricle on the right side This pattern is commonly called corrected transposition The second type of ventricular structure is rare and called isolated bulbar inversion In this type the inflow portions of the ventricles are normally placed but the out flow portions are inverted. This is characterized by the left ventricle s possessing an infundibulum (conus) from which the aorta arises while the right ventricle does not possess a conus and gives rise to the pulmonary trunk Since the atrioventricular (A V) valves are part of the respective ventricular inflow portions (sinuses) bulboventricular inversion carries with it inversion of the A V valves In isolated bulbar inversion there is no inversion of the A V valves since the inflow portions of the ventricles are normally placed. Therefore when the ventricles are inverted tricuspid atresia in an anatomic sense involves the left A V valve while with isolated bulbar inversion tricuspid atresia involves the right A V valve

The rarity of tricuspid atresia associated with l transposition prompts us to present five cases of this association In one of these there was classical bulboventricular inversion The other four were examples of isolated bulbar inversion

Among 50 specimens of heart with l transposition that we studied there were five instances in which the anatomic tricuspid valve was atretic Clinical roentgenologic electrocardiographic and pathologic findings were available in each case Cardiac catheterization studies and angiography had been performed in each patient

Four of the five patients were male and one was a female (Table I) Their ages ranged from two weeks to four months

Pathologic observations

Situs solitus of the viscera and atria was present in each case and in none were there splenic anomalies In each case l transposition was present The aortic valve lay anterior and to the left of the pulmonary valve and the aorta ascended to the left of the pulmonary trunk

The systemic and pulmonary venous connections were normal The morphologic right and left atria were normally situated. The coronary sinus entered the right atrium in each instance

Tricuspid atresia with bulboventricular inversion We observed one specimen of tricuspid atresia with bulboventricular inversion (Case 1)

From the Departments of Pathology and Pediatrics University f Minnesota M polis, and the Dep rtment of Path logy United Hosp tal M ll Divi ion, St. P l

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an associated anterior loop is indicative of a direct posterior infarction Aside from such in direct evidence, no distinctive differences were observed between these two groups No single cri terion or group of criteria established by previous investigators was able to separate the two groups The present experience would indicate that established criteria do not permit differen tiation between the vectorcardiogram of a pa tient with a direct posterior infarction and that of a normal individual with an anterior QRS loop

Summary

An attempt was made to distinguish the vec torcardiogram of a direct posterior myocardial infarction from an anterior horizontal loop that is known to occur in over 20 per cent of normal subjects Patients with anterior horizontal QRS loops and arteriographic evidence of complete oc clusion of the right coronary artery the posterior descending artery, or dominant left circumflex coronary artery were compared to normal in dividuals with anterior vector loops in the horizontal plane Nine patients were thought to have a direct posterior infarction 13 patients were thought to be normal The association of an abnormal frontal plane QRS loop indicative of a diaphragmatic infarction (5 of 9 patients) implied an associated direct posterior infarction Other wise no differences were observed in the two groups Specifically in the horizontal plane, the 20, 30, 40 50 and 60 msec vectors both mag nitude and direction were similar Also the max imum QRS vector, half area vector anterior ac cession time, QRS loop rotation, T loop angle and rotation and magnitude of the maximum an terior, maximum posterior, and maximum right ward vectors of the QRS loop were similar in both groups It appears therefore that the previously established criteria for the vectorcardiographic diagnosis of a direct posterior myocardial infarc tion in general, adequately describes the vector cardiogram of a direct posterior infarction, but fails to distinguish it from the anteriorly oriented vectorcardiogram of normal individuals which occurs frequently enough to make the impor tance of this distinction a practical clinical prob lem

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Fig 1 Case 1 Tricuspid atresia in l transposition with bulbo ventricular inversion *A* External view of the heart and great vessels A = aorta P T = pulmonary trunk *B*, Aorta (A) arising from the hypoplastic inverted anatomic right ventricle (R V) *C*, Interior of the inverted, anatomic left ventricle (L V) The right atrioventricular valve with anatomic features of a mitral valve (M) shows fibrous con tinuity with the pulmonary valve (P V) The ventricular septal defect (D) leads to the right ventricle

both appendages lay to the left of the great vessels in this case

In the remaining two specimens (Cases 4 and 5) the outflow of the left ventricle was divided by a muscular ridge into left anterior and right posterior compartments (Figs 4 and 5) The aorta arose from the left anterior and the pulmonary trunk from the right posterior compartment In one case a unicommissural type of pulmonary valvular stenosis was present There was pulmonary mitral valvular continuity in each In one case the apex of the heart pointed to the right side (Case 5)

Coronary arterial pattern Except for Case 2 the coronary arterial pattern was identical in the other four specimens with minor variations In each of the latter cases the right coronary artery arose from the right aortic sinus and the left cor

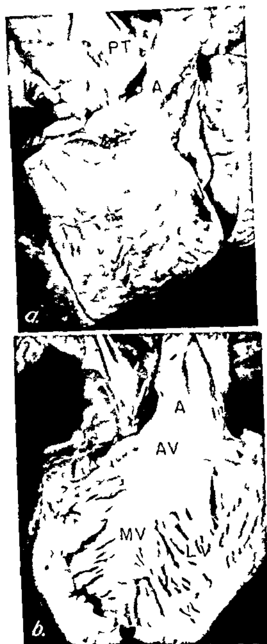


Fig 2 Case 2 Tricuspid atresia in l transposition with isolated bulbar inversion and pulmonary valvular atresia *A* External view of the heart and great vessels The aorta (A) lies anterior to and left of the pulmonary trunk (P T) The cardiac apex is directed toward the right *B*, Interior of the anatomic left ventricle (L V) The outflow portion shows a conus from which the aorta (A) arises The musculature of the conus separates the aortic valve (A V) from the mitral valve (M V)

onary artery from the posterior aortic sinus In three cases the anterior descending coronary artery usually a small branch arose from the right coronary artery In one specimen small anterior descending coronary arterial branches came off

Table 1 Summary of findings in cases reported

Case no	Age	Sex	Cyanosis	Anoxic spells	Murmurs	Electrocardiogram: Axis QRS	Electrocardiogram: Ventricular hypertrophy	Roentgenogram: Cardiac apex	Roentgenogram: Cardio megaly	Roentgenogram: Pulmonary vasculature	Anatomic findings: Ventricular morphology	Anatomic findings: Associated findings
1	6 wks	F	0	0	II/VI Ejection systolic	+100	0	Left	Moderate	Increased	Bulbo ventricular inversion	Coarctation subaortic stenosis PDA
2	2 wks	M	++	0	Absent	+75	Left	Right	Mild	Decreased	Isolated bulbar inversion	ASD PDA pulmonary atresia right apex right aortic arch
3	2 wks	M	+	0	Absent	0	Left	Left	Marked	Increased	Isolated bulbar inversion	ASD juxtaposition atrial appendages
4	4 mo	M	++	+	III/VI Ejection systolic	-50	Left	Left	Mild	Decreased	Isolated bulbar inversion	ASD pulmonary valvular stenosis
5	4 mo	M	++	+	II/VI Ejection systolic	+110	Right	Right	Moderate	Increased	Isolated bulbar inversion	Right apex

PDA = patent ductus arteriosus ASD = atrial septal defect.

The atretic A V valve lay between the left atrium and the left sided anatomic right ventricle The right sided A V valve, with features of a mitral valve entered a large right sided anatomic left ventricle (Fig 1) The hypoplastic anatomic right ventricle lay anterior and to the left of the anatomic left ventricle (Fig 1) It communicated with the left ventricle through a small muscular ventricular septal defect. The aorta arose from the conus of the anatomic right ventricle and the pulmonary trunk from the anatomic left ventricle There was pulmonary mitral valvular continuity

Tricuspid atresia with isolated bulbar inversion In the remaining four specimens there was isolated bulbar inversion and atresia of the right A V valve Certain features were in common among these cases The left A V valve exhibited features of a mitral valve in each It opened into a large ventricular chamber exhibiting morphologic features of a left ventricle in its inflow portion The outflow portion of the left sided ventricle formed a conus and in this way, resembled the outflow segment of an anatomic right ventricle The aorta arose above the conus so that there was absence of continuity between the aortic and mitral valves Structural differences among these cases follow

In one case (Case 2) the pulmonary valve was atretic A patent ductus arteriosus provided the pulmonary blood flow The right ventricle was represented by a slit like cavity below the atretic pulmonary valve The ventricular septum was intact The cardiac apex and the aortic arch were right sided (Fig 2)

In the second case (Case 3) the pulmonary trunk overrode the ventricular septum its valve forming the roof of a ventricular septal defect (Fig 3) The latter provided the only inlet for the right ventricle The right ventricle was normally positioned in relation with the left ventricle The sinus portion of the morphologic right ventricle was well formed but there was no outflow portion The aorta arose entirely from the left ventricle above a conus while the pulmonary trunk was biventricular in origin Mitral pulmonary valvular continuity was present. Juxtaposition of the atrial appendages was present in that



Fig 4 Case 4 Tricuspid atresia with l transposition and isolated bulbar inversion *A*, External view of the heart and great vessels. Aorta (A.) is transposed. *B*, Interior of the left ventricle (L. V) The aorta (A) arises above a conus separating the aortic valve from the mitral valve (M) The probe is through the stenotic pulmonary valve (out of view) *C*, Interior of the left ventricle (L. V) The mitral valve (M) is in fibrous continuity with the stenotic pulmonary valve P T = pulmonary trunk A. = aorta



Fig 5 Case 5 Tricuspid atresia with l transposition and isolated bulbar inversion *A* Aorta (A) lies anterior to and left of the pulmonary *trunk* (P T) The cardiac apex presents toward the right *B* Interior of the left ventricle (L. V) The outflow of the left ventricle is divided by a muscular ridge (arrow) into a posterior subpulmonary area and an *anterior* subaortic infundibulum (A I) The mitral valve (M) is in fibrous continuity with the pulmonary valve

stenosis The other two *each* with obstruction to pulmonary blood flow showed normal sized hearts with diminished pulmonary vasculature The cardiac apex pointed *toward* the right in two roentgenograms In one of these the cardiac configuration resembled a figure of eight and was nonspecific in the other case None of the roentgenograms showed features typical for l transposition The patient with atresia of the left A V valve did not show features characteristic of pulmonary venous hypertension

Angiocardiographic findings In the one case with atretic left A V valve (Case 1) an aortogram showed tubular hypoplasia of the aortic arch coarctation of the aorta and l transposition (Fig 6) Intracardiac studies were not performed in

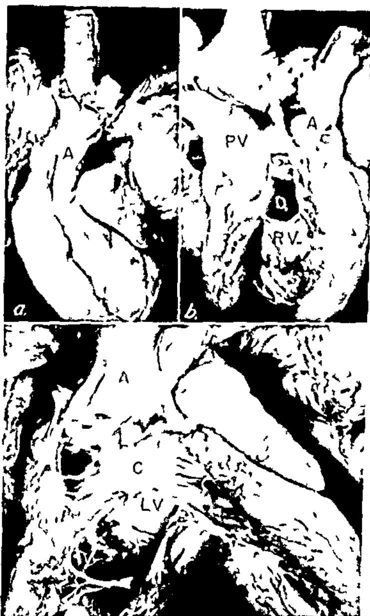


Fig 3 Case 3 Tricuspid atresia in l transposition with isolated bulbar inversion *A* External view The transposed aorta (A) hides the pulmonary trunk *B* Interior of the *anatomic right ventricle* (R V) *into which no atrioventricular valve opens* The inflow (sinus) portion of the right ventricle is well *formed and there is no conus* The pulmonary valve (P V) forms the roof of a ventricular septal defect (D) *The latter provides the inflow for the right ventricle C* The aorta (A) arises from the anatomic left ventricle (L V) above a conus *(C)*

from both the right as well as the left coronary artery The left coronary artery continued as the *posterior descending* in each of the four cases In Case 2 both coronary arteries arose from the right aortic sinus

Associated anomalies A large fossa ovalis atrial septal defect was present in three cases (Cases 2 3 and 4), the other two having a valve competent patent foramen ovale (Cases 1 and 5) The ductus arteriosus was patent in three cases

In the first case the patent ductus arteriosus was divided during the resection of coarctation of the aorta The latter *case also showed subaortic* stenosis and tubular hypoplasia of the aortic arch beyond the left subclavian artery The subaortic stenosis resulted from the narrow ventricular septal defect providing communication between the two ventricles (Table I)

Clinical observations

In each of the five infants a history of dyspnea was obtained The patient with atretic left A V valve (Case 1) was acyanotic whereas each of the other four patients were cyanotic A history of anoxic spells was present in two patients (Cases 4 and 5)

Signs of systemic venous congestion were present in each of the infants Evidence for *coarctation of the aorta was present in Case 1*, as indicated by a systolic pressure of 110 mm Hg in an arm and 60 mm Hg in a leg This was corrected surgically The cardiac size was normal in two patients and enlarged in three cases The *cardiac apex was on the right side of the thorax* in two patients (Cases 2 and 5) The first cardiac sound was normal and the second cardiac sound single and loud in each of the patients

In two patients murmurs were not present, while in the other three patients an ejection systolic murmur of grade II to III/VI intensity was audible along the sternum It was loudest *along the right side of the sternum* in one of the patients with the apex toward the right side (Case 5)

Electrocardiographic findings The frontal plane QRS axis was +100° in the one case with *bulboventricular inversion and atretic left* A V valve It was associated with right atrial hypertrophy There was no evidence for hypertrophy of either ventricle

In the four patients with atretic right A V *valve, the electrocardiogram showed* a frontal plane QRS axis varying from −50° to +110° The PR interval was prolonged in one case who was on digitalis Right atrial hypertrophy was present in one case and none showed left atrial hypertrophy *Three electrocardiograms* showed features of left ventricular hypertrophy and one of right ventricular hypertrophy

Radiologic findings Roentgenograms showed cardiomegaly with increased pulmonary vasculature in the three subjects without pulmonary

tion characterized by isolated bulbar inversion the atria and the inflow portions of the ventricles are normally positioned and only the outflow portions of the ventricles are inverted Raghib Anderson and Edwards[1] reported the first detailed description of such a case Van Praagh and Van Praagh[2] reported similar cases (Cases 1 and 2) as cases of anatomically corrected transposition In these cases however a subaortic as well as a subpulmonary conus was present preventing continuity of each semilunar valve with each A V valve The first case of the latter authors also exhibited tricuspid atresia

Pathologic findings in our cases indicated two types of inverted transposition One case (Case 1) is an example of the classic type of bulboventricular inversion In this case tricuspid atresia represents atresia of the left A V valve Our remaining four cases are examples of isolated bulbar inversion along with tricuspid atresia In these cases the atria and ventricles were in a normal relationship while the outflow portions of the ventricles were inverted resulting in an anterior left sided aorta arising from a well developed conus above a left sided morphologic left ventricular sinus Discontinuity between the aortic valve and mitral valve was present in each The patent A V valve showed features of a mitral valve The atretic valve therefore represents tricuspid atresia in these cases

In four cases of the present series the coronary arterial pattern was typical for inverted transposition The anterior descending as well as the circumflex arteries arose from the right aortic sinus and the left coronary artery which continued as the posterior descending arose from the posterior aortic sinus This finding was helpful in indicating inverted or l transposition in our cases

Keith Rowe and Vlad[3] introduced inverted transposition (l transposition) of the great vessels in the anatomic classification of tricuspid atresia In our collection of 45 specimens with atresia of the right A V valve l transposition constituted 8 8 per cent. On the other hand, in our collection of 50 cases of l transposition tricuspid atresia was present in five cases (10 per cent) a figure similar to that of Paul[4] In a series of 20 cases of corrected transposition the latter author found two cases associated with tricuspid atresia

It is known that in cases of tricuspid atresia

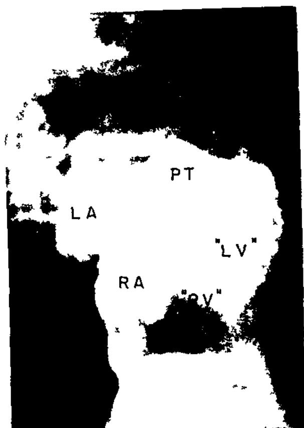


Fig 8 Case 3 Frontal view of venous angiocardiogram showing features of tricuspid atresia as well as l transposition. R. A = right atrium, L. A = left atrium L. V" = left ventricle R V = right ventricle P T = pulmonary trunk A = aorta.

the clinical and hemodynamic findings depend upon the relationship of the great vessels and the presence or absence of obstruction to pulmonary blood flow In cases with transposition of the great vessels an increased pulmonary flow is usually present whereas in cases with normally related great vessels obstruction to pulmonary blood flow is more frequent

Obstruction to pulmonary blood flow was present in two of four cases in our series in which the atretic A V valve was right sided Both showed moderate cyanosis clinically and decreased pulmonary vasculature in the thoracic roentgenograms

Our five cases of anatomic tricuspid atresia and l transposition represent two hemodynamically different situations In the four cases with the atretic right sided tricuspid valve the features are basically like those in classical tricuspid atresia with transposition of the great vessels. On the other hand, in the only case with



Fig 6 Case 1 Aortogram showing features of l transposition and coarctation of aorta A Frontal view B Lateral view



Fig 7 Case 2 Angiocardiogram showing features of l transposition A, Frontal view B Lateral view

this case Of the other four cases, each with an atretic right A V valve angiographic studies demonstrated transposition of the great vessels in each instance Features of l transposition, however, were correctly identified in only three of the four cases (Figs 7 and 8) The presence of obstruction to pulmonary blood flow was recognized in both patients in whom it was present (Cases 2 and 4)

Comment

In the classical type of inverted transposition of the great vessels (corrected transposition), the aorta lies anterior and to the left of the pulmonary trunk and arises from a morphologic right ventricle which is placed to the left side (inverted) It receives the saturated blood from the normally positioned left atrium

In an exceptional type of inverted transposi

Serum enzymes after cardiac surgery using cardiopulmonary bypass

J M Neutze MD FRACP
M J Drakeley MRCS LRCP FRCS
B G Barratt Boyes KBE ChM FRACS
Karen Hubbert
Auckland New Zealand

A number of investigators have demonstrated levels of serum enzymes after cardiac surgery considerably higher than those found after abdominal or thoracic surgery Initial suggestions that ventriculotomy liver damage or hemolysis may play an important role have not received general support Higher levels have been found in children than in adults and higher levels have been associated with prolonged cardiopulmonary bypass Some authors have concluded that high levels are part of a complex response of the whole organism [1] but others have suggested that myocardial damage plays an important role [2] If the latter possibility is sustained it emphasizes the need for continued attempts to improve myocardial support during cardiac surgery

Many of the studies have been carried out in a relatively small number of patients often of varied etiology creating difficulties in assessing the relative contributions of independent factors In the present study detailed investigations were made in a larger group of patients to permit analysis within each etiologic group in the hope that a clearer pattern would emerge

Methods

Protocol of study Observations were made on an unselected series of patients undergoing cardiac surgery using cardiopulmonary bypass between March and December 1972 Apart from three short interruptions because of technical factors the series was continuous and all patients admitted to the intensive care unit after cardiac surgery during the period of the study were included. Subsequently however data from 27 patients were rejected these included five patients who did not fit into a sufficiently large etiologic group for analysis (four with aortic valve replacement combined with coronary artery grafting and one with tricuspid valve replacement) eighteen patients from whom insufficient blood specimens had been collected three patients with mitral valve disease and one patient with rupture of a sinus of Valsalva aneurysm who were unusual for their etiologic group in that coronary perfusion was used during surgery One of these 27 patients died in the postoperative period but the other 26 patients survived and followed an unremarkable course

In 172 remaining patients the following observations were made preoperatively and on the first second and third postoperative days 13 lead electrocardiograms serum glutamic oxaloacetic transaminase (SGOT) serum lactic dehydrogenase (LDH) serum creatine phosphokinase (CPK) and serum alkaline phosphatase (AP) In 88 of the patients LDH isoenzymes were also measured At least one further electrocardiogram was recorded in all patients before discharge from the hospital and, where abnormalities were suspected, more frequent recordings were made All electrocardiograms were interpreted by one of us (J M N) knowing the clinical diagnosis but not the clinical status of the patient or the enzyme results The following data were also recorded cardiopulmonary bypass time aortic cross clamping time use of coronary artery perfusion peak

From the C rd ology Cardiotho ac c Surgery and B ochemi try Departments, Green La e Hospital, Auckland, New Zeala d.
Received for publ c tion Jan. 22 1974
Repri t requests to Dr J M Neutze Cardiology Department, Green Lane Hosp tal, Green Lan West, Auckland 3 New Ze la d.

atresia of the left A V valve representing anatomic tricuspid atresia the hemodynamic consequences resemble mitral atresia

An interesting finding in two of our cases with atretic right A V valve was the presence of an unusual frontal plane QRS axis for tricuspid atresia This consisted of right axis deviation (+110°) in one case (Case 5) and an axis of +75° in the other case (Case 2) Similar findings have been reported earlier in cases of tricuspid atresia associated with transposition of the great vessels [5] and in one case of tricuspid atresia with congenital absence of the pulmonary valve reported from this institution [6]

Summary

Five cases of tricuspid atresia with the rare association of l transposition are reported In one case classical ventricular inversion was present (bulboventricular inversion) and the tricuspid atresia involved the left A V valve

In the remaining four cases only the outflow portions of the ventricles were inverted (isolated bulbar inversion) The atretic tricuspid valve was right sided.

In addition to documenting rare anatomic states, this report identifies unusual electrocardiographic findings in tricuspid atresia Of two of four cases with atresia of the right A V valve the electrocardiogram showed right axis deviation (+110°) in one and a normal axis (+75°) in another

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Table II Changes in total LDH and isoenzymes (expressed as a percentage of the resting value) with storage of samples

	LDHT	*LDH1*	*LDH2*	*LDH3*	*LDH4*	*LDH5*
Samples stored at room temperature (N = 10)						
Day 1	−3 0	−4 7	−5 2	−0 2	−3 3	−3 3
Day 2	−2 6	−10 8	+2 5	+1 9	−2 0	−5 7
Day 3	−7 6	−9 0†	−7 6	−5 1	+0 5	−1 6
Samples stored at 4 C (N = 10)						
Day 1	−4 3	−3 6	−7 5†	−3 3	+12 1	+4 2
Day 2	−0 2	−5 5	+5 1	−3 3	+7 8	+9 1
Day 3	−7 4	−3 9	−1 0	−16 6†	−2 9	−6 6

S gn fica of changes 0 01 ⟨P ⟨0 05
†−0 005 ⟨ P ⟨ 0 01 by Student s p ired t test.

Table III Clinical details

Diagnosis	*No of patients*	*Average age*	*No aorta clamped*	*No coronary perfusion*	*Mean duration bypass (min.)*	*Mean duration aorta clamping (min.)*	*Peak hemolysis* (mg /100 mL)*
Aortic valve disease (AS 27 AI31)	58	50	58	58	117 (26)	103 (23)	39
Multiple valve disease (aortic and mitral 11 mitral and tricuspid 9 triple 2)	22	48	14	13	148 (38)	127 (52)	59
Mitral valve disease (MS 19 MI 21 valvotomy 14 replacement 26)	40	43	22	0	85 (36)	26† (24)	51
Congenital	27	19	13	0	58 (27)	36† (25)	34
Ischemic (single graft 4 double 6 triple 11 quadruple 1 aneurysm excision 3)	25	51	23	0	146 (47)	64† (45)	43
	172		130	71			

There wer fi e hosp tal de ths two patients with a rtic al e disease (th ee days and two weeks after operation) and three patients with multiple alve dise se (three weeks three mo ths and four months after peration) Enzymes were unremarkabl in ach case
AS = ortic stenosis, AI = a rti incompetenc MS = mitral steno is MI = mitral incompetence Majo an malies in patients with congen tal h art disease were atrial-septal defect 14 pulmonary stenosis fi e tetralogy of Fallot f ur ventricul septal defect two atrioventricular canal one left atrial myxom o e
Figures in p rentheses = standard deviati n.
Recorded during byp ss
†I termittent a rtic cross clamping

26 patients undergoing replacement) congenital heart disease (27 patients) and ischemic heart disease (25 patients) The aortic mitral and ischemic groups were all fairly homogeneous and contrast differences in anatomy and surgical technique The multiple valve group contained 13 patients in whom coronary artery perfusion was used for aortic valve replacement and nine patients in whom coronary artery perfusion was not required the congenital group included 13 patients in whom aortic cross clamping was required and 14 patients in whom it was not Subdivision of these two groups was not thought warranted but comment is made below on the effect of these differences in surgical technique

Results

Serum enzymes Results of enzyme studies are shown in Figs. 1 through 9 The statistical significance of the differences between diagnostic groups is shown in Table IV

Resting values of AP were higher in patients

Table I Variation in duplicate estimates of LDH isoenzymes (39 samples) assessed by linear regression

	LDH1	*LDH2*	*LDH3*	*LDH4*	*LDH5*
Mean values	37 9	29 3	17 0	8 2	9 7
Correlation coefficient	0 9804	0 9676	0 8841	0 8858	0 9179
S D	6 1	4 2	4 5	2 8	2 7

S D = standard deviation about the line of regression

hemolysis during bypass, complications during and after surgery, and postoperative status and treatment

For comparative purposes SGOT, CPK, AP, LDH and LDH isoenzymes were recorded for three successive days in 14 patients with acute myocardial infarction and in 13 patients with acute myocardial ischemia

Surgical techniques Cardiopulmonary bypass was carried out at 30° C to 32° C using a Kay Cross rotating disc oxygenator, except in patients with ischemic heart disease when a Temptrol disposable blood oxygenator was used

Continuous coronary perfusion was used in all patients with aortic valve disease using self inflating balloon tipped cannulae and individual roller pumps and maintaining a coronary line pressure of 100 mm Hg Where possible, sinus rhythm was maintained but when cardiac action failed or inefficient coronary perfusion was recognized, the coronary perfusate was cooled further by a separate heat exchanger to 26° C Coronary perfusion was also used for patients with multiple valve disease requiring aortic valve replacement, although perfusion was sometimes interrupted temporarily to improve exposure during insertion of the mitral valve prosthesis Where tricuspid valve replacement was also required, the patient was re warmed, the aorta was closed and unclamped and the prosthesis was inserted with the heart beating at normothermia

Isolated mitral valve surgery was carried out with the heart fibrillating In patients with associated mild aortic incompetence periods of aortic cross clamping usually of 15 to 30 minutes' duration, were used

In 13 patients with congenital heart disease intermittent aortic cross clamping was required for 20 to 30 minute periods with the myocardium at a temperature of 26° C to 30° C Care was taken to exclude air from the coronary arteries before releasing the aortic cross clamp

During the period of the study, two patients with ischemic heart disease underwent coronary artery bypass surgery without aortic cross clamping, but in the remainder of the patients *intermittent ischemic arrest was used* The maximum period of arrest was 37 minutes (at 30° C) and a five minute recovery period was allowed between each period of arrest keeping the heart fibrillating throughout. In all groups elective fibrillation was induced electrically and the current was then turned off

Enzyme studies Serum SGOT, LDH, CPK and AP were estimated by standard techniques[3-6] For the estimation of LDH isoenzymes the method of cellogel electrophoresis (Chemetron Milano) was modified to facilitate the handling of a relatively large number of samples Using a microzone technique, eight samples were tested in each batch Serum was applied with a 0 25 microliter applicator to a buffer soaked membrane Samples were electrophoresed by the application of seven amperes for 20 minutes The membrane was placed on a glass plate, covered with substrate and dye incubated at 37° C for 15 minutes, and then cleaned and dried Isoenzyme bands were read densitometrically with a Beckman scanner

To check reproducibility of measurements 39 duplicate samples were estimated in separate batches (Table I) Reproducibility was acceptable, bearing in mind that absolute values in many of these samples were small

For staffing purposes it was desirable to make measurements only on five days of each week The reported stability of the isoenzymes with storage[7] was checked by storing samples either at room temperature or at 4° C and making serial daily estimations The results (Table II) showed that changes in the first two days were minor and acceptable, but by Day 3, larger changes were not infrequent, especially in samples stored at 4° C Samples were, therefore stored at room temperature for a maximum of two days before measurement

Clinical details Clinical and surgical details are given in Table III The patients were divided into five groups aortic valve disease (58 patients all having valve replacement), multiple valve disease (20 patients having double and two patients having triple valve replacement), mitral valve disease (14 patients undergoing valvotomy and

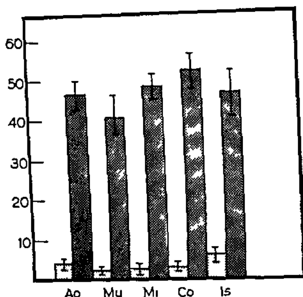


Fig 3 CPK levels in each diagnostic group Figures shown are micromoles per milliliter per hour normal range 0 5 to 4

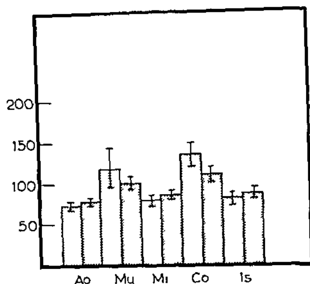


Fig 4 Alkaline phosphatase levels in each diagnostic group Figures shown are micromoles per milliliter per minute normal range 30 to 85

Table IV Statistical significance of the differences between groups in peak postoperative enzyme levels (Figs 1 through 9) Comparison is by Student s unpaired t test and the probability that the difference between the high value (left column labeled high value) and the low values (right columns labeled Ao Mu Mi Co and Is) occurred by chance is less than the figure given For example the probability that the difference between SGOT values in the aortic and mitral groups (illustrated in Fig 1) occurred by chance is less than 0 001 See Fig 1 for abbreviations

	High value	*Ao*	*Mu*	*Mi*	*Co*	*Is*
SGOT	Ao			0 001		0 005
	Mu			0 01		
	Co			0 05		
LDH	Ao		0 05	0 001	0 001	0 001
	Mu			0 005	0 005	0 005
AP	Mu	0 001		0 001		0 05
	Co	0 001		0 01		0 01
LDH1	Ao			0 05	0 05	0 05
	Mu				0 05	0 05
LDH2	Ao				0 05	0 05
	Mu				0 01	0 01
LDH3	Mu			0 005	0 001	0 001
LDH4	Mu			0 01	0 05	0 05
LDH5	Ao				0 05	
	Mu			0 05	0 005	

ocardial infarction as outlined above The high LDH (1 + 2) fractions probably indicated greater sensitivity of this measurement in detecting myocardial damage under these clinical circum stances.

Levels in 88 patients before and after cardiac surgery Details are shown in Table VI There was no significant difference within any diagnostic group in LDH (1 + 2) fractions before and after surgery There was however considerable varia

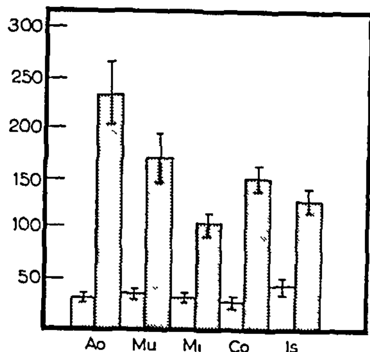


Fig 1 SGOT levels in each diagnostic group The barographs show the mean value of the group light shading indicating the preoperative level and dark shading the peak postoperative level Bars indicate ± 1 standard error of the mean. Figures shown are micromoles per milliliter per minute (M I U /ml) normal range 10 to 50 The statistical significance of the difference between groups is given in Table IV Ao = Aortic Mu = multiple Mi = mitral Co = congenital and Is = ischemic

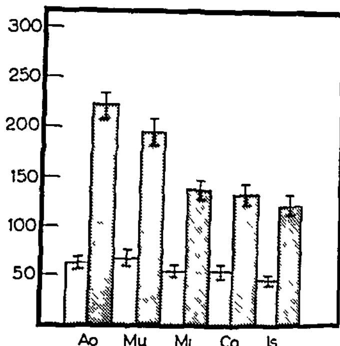


Fig 2 Total LDH levels in each diagnostic group Figures shown are micromoles per milliliter per minute normal range 20 to 50

with multiple valve disease (possibly because of liver impairment) and in patients with congenital heart disease (probably related to the number of younger patients) The differences between groups in resting values of other enzymes were sometimes significant but always small

Peak postoperative values for SGOT LDH and LDH isoenzymes were higher in the aortic and multiple groups than in the mitral congenital or ischemic groups This trend was apparent with each enzyme but was most clear cut for total LDH Peak postoperative values of AP remained marginally higher in patients in the multiple and congenital groups while peak postoperative CPK levels were high in all groups

Peak postoperative SGOT and LDH values correlated significantly with each other in all groups, correlation coefficients ranging from 0 8369 for patients with aortic disease to 0 5120 for patients with ischemic disease SGOT and CPK values correlated with each other more weakly in patients with aortic, mitral and ischemic disease, and LDH and CPK values correlated with each other weakly in patients with aortic disease only AP values did not correlate with those of any other enzyme

CPK and AP did not add significant information and are not considered further

Contribution of LDH isoenzymes

Patients with myocardial infarction or myocardial ischemia Details are shown in Table V Prior analysis indicated that the best index of myocardial damage was the ratio

$$\frac{LDH_1 + LDH_2}{\text{Total LDH}}$$

Satisfactory separation of isoenzymes was confirmed by the high LDH (1 + 2) fractions in 14 patients with myocardial infarction diagnosed on the basis of a history of prolonged chest pain, pathologic Q waves and ST T changes in the electrocardiogram and elevated total SGOT and LDH levels An LDH (1 + 2) fraction of 70 per cent or more gave strong supporting evidence of myocardial damage

High LDH (1 + 2) fractions were sometimes seen in the 13 patients described as suffering from myocardial ischemia These patients were admitted with chest pain two patients had congestive heart failure and four patients had arrhythmias but none satisfied the criteria for my

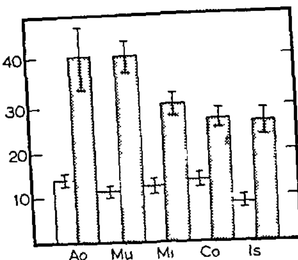


Fig 7 LDH3 levels in each diagnostic group

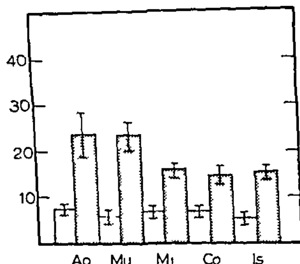


Fig 8 LDH4 levels in each diagnostic group

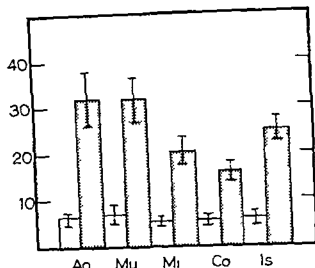


Fig 9 LDH5 levels in each diagnostic group

Table VI Percentage of preoperative and peak postoperative LDH contributed by LDH1 + LDH2 in 88 patients

	Preoperative	*Postoperative*
Aortic	55 8 (8 8)	61 9 (13 0)
Multiple	58 2 (5 7)	56 6 (15 6)
Mitral	60 5 (8 2)	55 4 (12 2)
Congenital	54 7 (7 6)	57 1 (6 9)
Ischemic	53 2 (16 1)	54 2 (10 8)

Figures given are the means and standard deviations.

Possible causes of high postoperative SGOT and LDH levels.

Age There was no correlation either within groups or in the total group of patients between age and SGOT or LDH levels

Perfusion. Inspection of Table III suggests that neither the duration of cardiopulmonary bypass nor the duration of aortic cross clamping where this was used, was likely to have an important influence on enzyme levels in the overall group of patients.

(1) SGOT levels correlated with bypass time only in the aortic group (R = 0 4964 P < 0 001) and in the congenital group (R = 0 551 0 001 < P < 0 01) Values for LDH were similar

(2) SGOT levels correlated with the duration of cross clamping of the aorta only in the aortic group (R = 0 3840 0 001 < P < 0 01) and in the mitral group (R = 0 4599 0 001 < P < 0 01) Values for LDH were similar For patients with aortic disease the duration of aortic cross clamping (Table III) was only slightly longer than the duration of coronary perfusion

(3) There was no correlation between enzyme levels and plasma hemoglobin levels during bypass in any diagnostic group

Factors during the first three postoperative days Thirty eight patients required intermittent positive pressure ventilation 20 patients required isoprenaline infusion for low cardiac output 17 patients had important bleeding nine patients had severe congestive heart failure eight patients required epicardial pacing six patients showed some sign of cerebral damage three

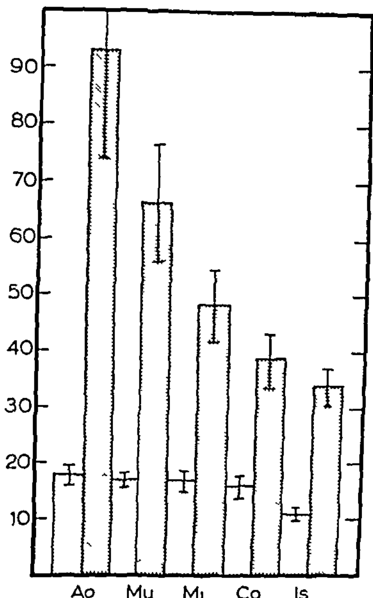


Fig 5 LDH1 levels in each diagnostic group

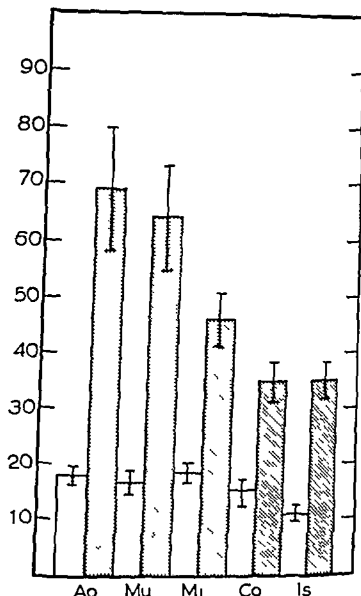


Fig 6 LDH2 levels in each diagnostic group

Table V Serum enzymes in 14 patients with myocardial infarction and 13 patients with myocardial ischemia

	Myocardial infarction	*Myocardial ischemia*	*Significance*
SGOT	146 (99)	49 (21)	0 001 < P < 0 005
LDH	154 (83)	85 (57)	0 01 < P < 0 05
Percent LDH 1 + 2	76 (8 6)	66 (7 5)	0 001 < P < 0 005

Percent LDH 1 + 2 = percentage of total LDH contributed by LDH 1 + 2
Significance = significance of differences between the two groups assessed by Student s unpaired t test
Figures given for enzyme values are the means and the standard deviations (in parentheses)

tion in both preoperative and postoperative values for LDH (1 + 2) fractions In the case of preoperative levels, this represents the expected variation where total LDH values are relatively low High postoperative levels of total SGOT and LDH were commonly, but not always associated with high LDH (1 + 2) fractions (Table VII) The fact that the majority of patients showed total SGOT and LDH levels far above normal without high LDH (1 + 2) fractions argues that myocardial damage accounted for only part of the total enzyme rise

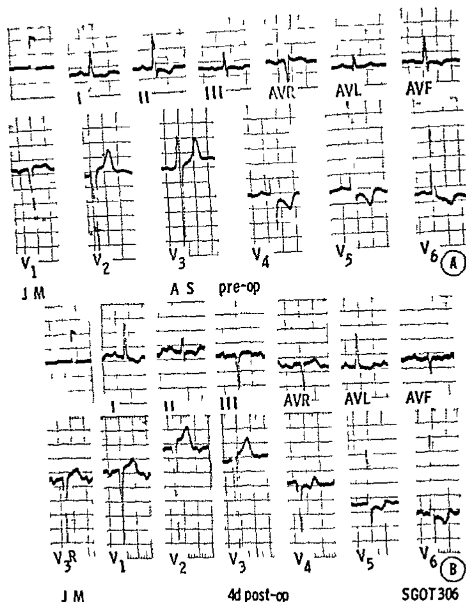


Fig 11 Electrocardiogram showing myocardial damage (aortic Case 12 Table VII) preoperative record and tracings taken on the fourth and thirteenth postoperative days Note (1) progressive loss of voltages in inferior leads and (2) loss of voltage in central chest leads with some variation in recordings of individual leads This tracing illustrates the minimal change accepted as showing "myocardial damage"

bundle branch block or intramural block (three patients) development of left anterior fascicular block (two patients) development of unexplained right bundle branch block (one patient) marked prolongation of the PR interval (one patient) development of complete heart block (one patient) or extreme depression of ST and T segments with minor loss of voltage of R waves (three patients)

The development of isolated moderate or marked ST T segment change as described by Hultgren and co workers[8] was not accepted for reasons described below The distinction between myocardial damage and probable myocardial damage is arbitrary Diagnoses based on voltage changes were relatively straightforward and were obvious in most patients with careful inspection Diagnoses based on conduction anomalies however presented some difficulty In some cases the anomaly could have occurred as a result of local surgical trauma, for example left bundle branch block or complete heart block occurring after aortic valve replacement. In other

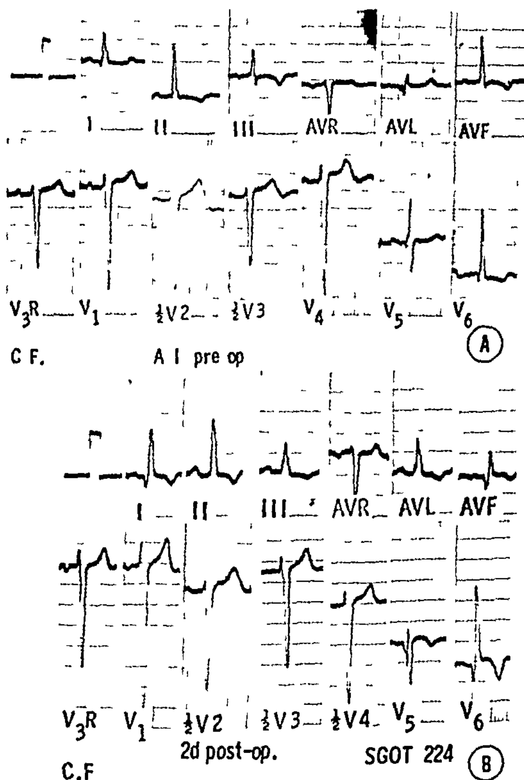


Fig 10 Electrocardiogram showing myocardial infarction (aortic Case 17 Table VII) preoperative record and tracing taken on the second postoperative day Note lateral and diaphragmatic changes This tracing illustrates the minimal change accepted as myocardial infarction

patients suffered cardiac arrest and three pa tients had marked jaundice High enzyme levels occurred in each of these groups of patients but none of these factors had a discernible influence on enzyme levels

Myocardial damage at operation This was assessed by serial electrocardiograms as follows

(1) Myocardial infarction pathologic Q waves and ST T changes (eight patients) (2) Myocardial damage marked loss of voltage of R waves con sistent in serial tracings but without pathologic Q waves (six patients) (3) Probable myocardial damage modest loss of R waves consistent in serial tracings (12 patients) development of left

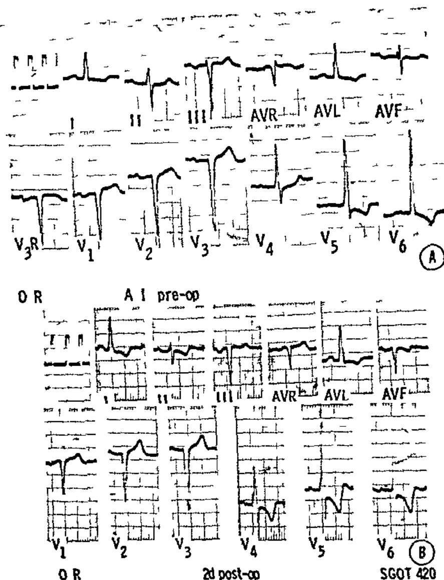


Fig 12. Electrocardiogram showing probable myocardial damage (aortic Case 11 Table VII) preoperative record and tracing taken on the second postoperative day Note loss of voltage in inferior leads The change was minimal but, as it was quite consistent in serial tracings it was accepted as indicating probable damage This tracing illustrates the minimal abnormality accepted for this diagnosis Where minor changes were not consistently present in serial tracings the postoperative record was passed as normal Moderate depression of ST and T segments is evident in the postoperative tracing but these changes were not accepted as evidence of myocardial damage in the absence of voltage changes

recognized in any patient in the multiple group and the levels of SGOT and LDH in this group were not significantly higher in those requiring coronary perfusion than in those who did not (Fig 13)

(3) Ventricular fibrillation during operation Most patients in the mitral congenital and ischemic groups were in ventricular fibrillation throughout most of the operative procedure and no differences were evident compared with those patients who remained in sinus rhythm in these groups In the aortic group however SGOT and LDH levels were much higher and electrocardiographic abnormalities were much more common in those patients with ventricular fibrillation for at least half the duration of coronary perfusion compared with those patients who remained in sinus rhythm through most or all of the operation (Table IX) Differences in LDH levels were similar These differences may be

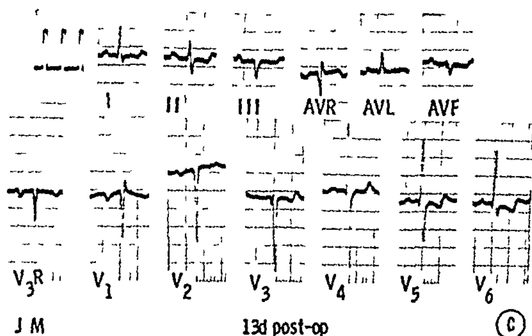


Fig 11 C For legend see page 433

cases local trauma was not easily incriminated. Rather than attempt an artificial distinction significant conduction anomalies were taken as evidence of probable myocardial damage unless as with the development of right bundle branch block after patch closure of the ventricular septal defect in tetralogy of Fallot, they were expected almost routinely This group may therefore, include a few false positive results but in most cases the presence of myocardial damage was virtually certain Examples of electrocardiographic changes are shown in Figs 10 through 12

Of 34 patients with a peak postoperative SGOT level greater than or equal to 200 units per milliliter, seven patients showed the electrocardiographic pattern of myocardial infarction four patients showed myocardial damage 16 patients showed probable myocardial damage and seven patients showed no change (Table VII) Of 138 patients with an SGOT level less than 200 units per milliliter, one patient showed the pattern of myocardial infarction one patient myocardial damage, seven patients probable myocardial damage and 129 patients no change In the nine patients of this group showing electrocardiographic abnormalities SGOT ranged from 48 to 178 with an average of 98 units per milliliter The difference in the incidence of normal and abnormal electrocardiograms in patients with SGOT levels above and below 200 units per milliliter was highly significant ($P < 0.001$) It was concluded that myocardial damage was the major cause of high SGOT levels The relationship between abnormal electrocardiograms and high levels of LDH was very similar

Abnormal or probably abnormal electrocardiograms were found in 21 per cent of the total group of patients the incidence being highest in the aortic group with 33 per cent, and lowest in the mitral and congenital groups (Table VIII) In the aortic and multiple groups all but one patient with evidence of myocardial damage had an SGOT level of 200 or greater but this was not true of the other groups

The possible causes of myocardial damage were as follows

(1) Factors intrinsic to bypass the weak correlation between the duration of cardiopulmonary bypass and of aortic cross clamping on the one hand and enzyme levels on the other hand has already been noted Neither factor could be incriminated as a major cause of high enzyme levels

(2) Problems with coronary perfusion Poor coronary perfusion was recognized at operation in five patients An additional four patients had low right coronary flows, in these patients it was not possible to distinguish between faulty perfusion, and low flow due to an anatomically small right coronary artery Seven of these nine patients showed raised enzyme levels (Table VII) and six patients showed electrocardiographic abnormalities Poor coronary perfusion was not

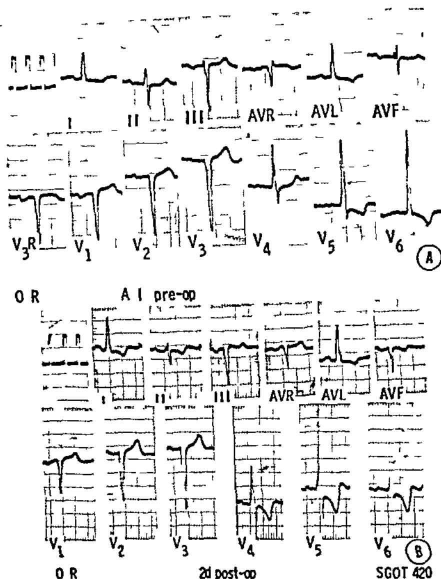


Fig 12. Electrocardiogram showing probable myocardial damage (aortic Case 11 Table VII) preoperative record and tracing taken on the second postoperative day Note loss of voltage in inferior leads The change was minimal but, as it was quite consistent in serial tracings it was accepted as indicating "probable damage " This tracing illustrates the minimal abnormality accepted for this diagnosis. Where minor changes were not consistently present in serial tracings the postoperative record was passed as normal Moderate depression of ST and T segments is evident in the postoperative tracing but these changes were not accepted as evidence of myocardial damage in the absence of voltage changes

recognized in any patient in the multiple group and the levels of SGOT and LDH in this group were not significantly higher in those requiring coronary perfusion than in those who did not (Fig 13)

(3) Ventricular fibrillation during operation Most patients in the mitral congenital and ischemic groups were in ventricular fibrillation throughout most of the operative procedure and no differences were evident compared with those patients who remained in sinus rhythm in these groups In the aortic group however SGOT and LDH levels were much higher and electrocardiographic abnormalities were much more common in those patients with ventricular fibrillation for at least half the duration of coronary perfusion compared with those patients who remained in sinus rhythm through most or all of the operation (Table IX) Differences in LDH levels were similar These differences may be

Table VII Details of 34 patients with peak SGOT 200 units or greater after cardiac surgery peak postoperative enzyme values

No	SGOT	LDHT	LDH 1+2	Difficulties with coronary perfusion	Postoperative features	ECG myocardial damage
Aortic valve disease						
1	810	500				Damage
2	810	910			Mild hypotension	Probable I B
3	810	948	78	Bifurcation left coronary	Difficult resuscitation	Infarct
4	738	400	81	Poor right coronary perfusion		Infarct
5	720	220				Probable C H B
6	712	660	82	Bifurcation left coronary	Difficult resuscitation	Infarct
7	648	444			Ventricular fibrillation	Probable A F B
8	570	576	68	Poor right coronary perfusion		Probable V
9	528	291				Damage
10	522	247		Poor right and left coronary perfusion		Probable V
11	420	244				Probable V
12	306	294	81			Damage
13	300	200	77	Poor right coronary perfusion	Mild right hemiplegia	Nil
14	300	322				Infarct
15	282	320	59		Possible air embolism	Nil
16	258	180	68			Probable V
17	224	155	64	Bifurcation left coronary		Infarct
18	220	305				Probable RBBB
19	205	206				Probable V
20	200	167	64			Probable LBBB
Multiple valve disease						
1	474	276	40			Probable V
2	450	394	58			Infarct
3	360	266	65			Probable 1st deg HB
4	346	200			Mild hypotension	Probable V
5	268	194	35			Nil
Mitral valve disease						
1	390	320	78		Difficult resuscitation	Damage
Congenital						
1	348	128	64			Nil
2	318	188	57			Nil
3	254	248	59		Possible air embolism	Probable A F B
4	258	153	57			Nil
Ischemic						
1	270	250				Probable V
2	242	155	48			Probable V
3	228	139	54			Infarct
4	200	114			Mild hypotension	Nil

LDHT = total LDH
LDH1 + 2 = percentage of total LDH contributed by LDH1 and LDH2 combined.
ECG myocardial damage = evidence in serial electrocardiograms of myocardial damage at operation (see text)
Bifurcation left coronary = early bifurcation interfering with coronary perfusion.
A F B = anterior fascicular block
C H B = complete heart block
1st deg HB = first degree heart block
I B = Intramural block
LBBB = left bundle branch block
RBBB = right bundle branch block.
V = voltage change

Table VIII Patients with electrocardiographic evidence of infarction myocardial damage or probable myocardial damage after cardiac surgery

	Aortic	Multiple	Mitral	Congenital	Ischemic	Total
No of patients	58	22	40	27	25	172
No of abnormal ECG s	19	4	5	2	6	36
No with abnormal ECG s and SGOT < 200	1	0	4	1	3	9

Table IX Effects of ventricular fibrillation and poor coronary perfusion in 50 patients undergoing aortic valve replacement

	Sinus rhythm		Ventricular fibrillation		Significance
	Number	Mean	Number	Mean	
A Whole group					
SGOT	31	161 (32)	19	300 (49)	0 001 < P < 0 01
Normal ECG	26		8		
Abnormal ECG	5		11		0 001 < P < 0 01
B Omitting nine patients with probable faulty coronary perfusion					
SGOT	29	139 (27)	12	228 (39)	Not significant
Normal ECG	26		5		
Abnormal ECG	3		7		0 001 < P < 0 01

Significance = significance of the differences between the two groups assessed by Student s unpaired t test for enzyme values and differences in proportions for electrocardiographic changes Figures given for enzyme values are the means and standard errors of the means (in parentheses)

partly explained by the effect of poor coronary perfusion in some patients Considering only those patients in whom coronary perfusion appeared satisfactory electrocardiographic abnormalities were still more common in those patients with ventricular fibrillation but differences in enzyme levels were no longer significant (Table IX)

There was no significant difference between enzyme values in patients with aortic stenosis and in patients with aortic incompetence (Fig 13) It is noteworthy that enzyme values in patients in the aortic group who remained in sinus rhythm through most of the operative procedure were only slightly higher than those found in the mitral congenital, or ischemic groups

Discussion

There is general agreement that enzyme rises after abdominal surgery thoracotomy or closed valvotomy are modest and that an SGOT level of 60 units is strongly suggestive of myocardial infarction [9,13] Much higher levels of SGOT and LDH have been reported after surgery involving cardiopulmonary bypass Neither anesthesia nor hemolysis appears to play a significant role [1,14] Some authors have found slightly higher levels in younger patients [2,15] but this has not been generally confirmed. A correlation between serum enzyme levels and the duration of cardiopulmonary bypass has been described in some groups[1,8,15,17] but not in others [12,18,19] Higher levels with operations requiring ventriculotomy have been reported by some authors[12,15,18,20] but not by others [1,11] Hepatic damage was suggested as a major cause of the rise in SGOT levels[18] but this has not been confirmed.[1,2,16,20,21] Quinn and coworkers[12] found that potassium induced cardiac arrest produced much higher levels of serum glutamic oxaloacetic transaminase

The results of many of the earlier investigations have been summarized by Welbourn Melrose and Moss [2] While most of these studies were carried out in a relatively small number of patients of diverse etiology it may be concluded that the type of anesthetic age of the patient, degree of hemolysis during operation and the degree of surgical trauma and hepatic damage

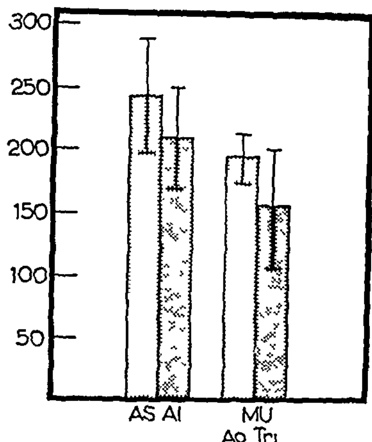


Fig 13 Peak postoperative SGOT levels in patients with aortic and multiple valve disease The barographs show the mean values for each group and bars ± 1 standard error of the mean *AS = aortic stenosis AI = aortic incompetence* Mu/Ao = multiple valve disease involving aortic valve replacement (using coronary perfusion) *Mu/Tri* = mitral and tricuspid valve replacement (without coronary perfusion)

Table X

	No of patients	*Mean SGOT level*
ECG abnormal by our criteria (most of which showed ST T *changes)*	24	365
ECG abnormal as judged by ST T change only	32	105

show little correlation with early postoperative enzyme changes, but that there is some correlation with the duration of cardiopulmonary bypass and that a considerable proportion of the enzymes come from myocardial tissue This was recently confirmed by Hultgren and co workers[8] who produced further evidence that myocardial damage was the main cause of unusually high SGOT and LDH levels

In the present study, the patients were divided into those groups with aortic valve, multiple valve, mitral valve, congenital, or ischemic heart disease, and each factor was examined within the five individual groups Patients with aortic or multiple valve disease had higher postoperative SGOT and LDH levels than patients with mitral congenital, or ischemic disease There was no evidence that the results were affected by age or hemolysis on bypass and there was no general correlation between high levels and postoperative factors including ventilation, low cardiac output with isoprenaline infusion, hemorrhage, congestive heart failure, epicardial pacing cerebral damage cardiac arrest, or jaundice Enzyme levels correlated with cardiopulmonary bypass time in the case of patients with aortic and congenital heart disease and with the duration of aortic cross clamping in patients with aortic and mitral disease These correlations were weak and had little effect on individual enzyme levels

Baseline elevation of enzymes in all groups was confirmed and the result of LDH isoenzyme studies supported the contention that many tissues are involved The reliability of a disproportionate rise in LDH 1 and 2 isoenzymes with myocardial infarction is well established[22 24] and the reliability of the technique used in the present study was confirmed by the pattern seen in a small group of patients with myocardial infarction By contrast most of the postoperative patients showed a rise in all isoenzymes A disproportionate rise in LDH 1 and 2 was seen in some patients with myocardial damage, but in many patients the LDH 1 and 2 fractions did not approach the level seen in myocardial infarction even though there was unequivocal evidence of myocardial damage on other grounds Isoenzyme studies did not, therefore, prove helpful in the detection of myocardial damage in this situation

The correlation between electrocardiographic and enzyme evidence showed that high SGOT and LDH levels could usually be explained by myocardial damage Twenty seven out of 34 patients with an SGOT level equal to or greater than 200 units per milliliter showed electrocardiographic evidence of myocardial damage while only nine out of 138 patients with an SGOT level less than 200 showed such damage LDH and SGOT levels correlated closely

Electrocardiographic evidence of definite or probable myocardial damage was found in 33 per cent of patients in the aortic group 18 per cent in

the multiple group 13 per cent in the mitral group seven per cent in the congenital group and 24 per cent in the ischemic group Average peak postoperative SGOT levels in patients from the aortic and multiple groups with electrocardiographic abnormalities were 478 and 408 by contrast average values in the patients from these groups without electrocardiographic abnormalities were 155 and 118 similar to values found in the other groups With one exception peak postoperative SGOT levels in patients in the aortic and multiple groups who showed electrocardiographic abnormalities were greater than 200 units per milliliter This was not true in patients from the other groups where the average peak postoperative SGOT level in patients showing electrocardiographic abnormalities was about 100 units per milliliter Whether myocardial damage was more extensive in the aortic and multiple groups or whether enzyme release was greater simply because of greater muscle mass cannot be determined from the data

In addition to the presence of marked left ventricular hypertrophy patients in the aortic group and 13 out of the 22 patients in the multiple group had coronary perfusion at operation whereas this technique was not used in any other patient in the present study Bloodwell and co workers[25] and Littler and co workers[17] reported little difference in SGOT levels in patients who underwent aortic valve replacement with coronary perfusion compared with those patients whose coronaries were not perfused and the results of Hultgren and co workers[8] confirm the adequacy of myocardial protection in most cases with the use of superficial myocardial cooling In the present series high levels of enzymes, often associated with abnormal electrocardiograms followed ventricular fibrillation during surgery It was noted, however that ventricular fibrillation and subsequent myocardial damage often followed faulty coronary perfusion and it is likely that poor regional perfusion occurred in other cases the production of myocardial damage by unequal coronary perfusion is well established.[26] Microemboli in the coronary perfusion circuit may be an additional cause of ischemic damage In the present series, a 100 to the inch mesh filter was used in the circuit. Thrombus formation on the filter was observed on occasion but correlation with subsequent myocardial damage was not attempted. Thus while coronary perfusion appears to give satisfactory myocardial protection in most patients it has been associated with a significant incidence of serious complications

In the multiple group lower enzyme levels had been anticipated in patients undergoing mitral and tricuspid replacement than in those in whom aortic replacement was also required. This was generally true but high values in two patients after mitral and tricuspid valve replacement prevented a statistical distinction The numbers involved are small and no firm conclusion is warranted on the available data

The congenital group is a composite group 14 patients having pulmonary stenosis or atrial septal defect and 13 patients having more complex lesions When these two subdivisions are compared those with more complex lesions had longer perfusion times (76 minutes as compared with 39 minutes) higher SGOT levels (182 as compared with 102) and higher LDH levels (155 as compared with 112) Nevertheless electrocardiographic abnormalities and exceptionally high enzyme levels were rare in the overall group

Twenty four per cent of patients in the ischemic group showed electrocardiographic abnormalities a figure comparable with other reports[27, 28] Coronary arteriography was carried out three weeks postoperatively in 14 of the 25 patients One of the two or more vein grafts was occluded in six patients and three of these patients showed probable myocardial damage electrocardiographically All grafts were patent in eight patients none of whom showed electrocardiographic abnormalities Correlation between graft occlusion and electrocardiographic abnormality has been reported[28] but is not always found.[27]

SGOT levels in the present study were higher than those reported by Hultgren and co workers[8] who recorded values in 126 patients of whom 102 underwent valve replacement Thirty two per cent of Hultgren and co workers patients had a postoperative SGOT level greater than 90 units per milliliter and 70 per cent of these patients were considered to show evidence of myocardial damage Only 10 per cent of the patients with an SGOT level of less than 90 units per milliliter showed such evidence By contrast, 69 per cent of our patients had an SGOT level over 90 units per milliliter but only 30 per cent of these patients were regarded as showing electrocardiographic evidence of myocardial damage

The method of estimating SGOT levels and the units used were comparable One major difference in the two series is the use of coronary perfusion in the present study This cannot explain the difference in enzyme levels however, as 66 per cent of our patients in the mitral congenital, and ischemic groups in whom coronary perfusion was not used, had SGOT levels greater than 90 units per milliliter It must be concluded that some other difference in patient selection or in surgical technique is involved It is possible that the use of a rotating disc oxygenator in all but the ischemic group of the present series contributed to the difference A higher incidence of emboli with the rotating disc oxygenator than with the disposable bubble oxygenator is well documented[29] and the latter is now used for all patients

Assessing the postoperative electrocardiogram is not straightforward, for while there is unlikely to be any discrepancy in the diagnosis of myocardial infarction varying criteria have been used for assessing lesser degrees of myocardial damage In the present series this assessment was based on loss of QRS voltages or unexplained conduction anomalies It was accepted that some false positives would occur where a conduction anomaly resulted from purely local surgical trauma but it was felt wiser to include all such anomalies in preference to attempting some artificial separation in the event it was surprising how often such conduction anomalies were associated with high enzyme levels In the study of Hultgren and co workers [8] myocardial damage was diagnosed in many patients on the basis of ST depression greater than 2 mm , with or without T wave inversion This change is particularly common in patients with severe left ventricular hypertrophy especially in those patients who are digitalized preoperatively, and such changes were not accepted in the present series Most cases satisfying our criteria showed ST and T wave changes (a borderline example is shown in Fig 11) but many patients showed ST and T wave changes without satisfying our criteria For comparison, patients in our series undergoing valve surgery were assessed by two sets of criteria (Table X)

This difference is highly significant (P < 0 001) By contrast there was no significant difference in the SGOT levels in patients satisfying our criteria whether or not ST or T changes were present Although ST T changes may unquestionably indicate myocardial damage these results indicate that ST T criteria in isolation should be used with extreme caution in the postoperative period

In most cases the myocardial lesions demonstrated played no discernible role in postoperative progress and indeed most would have escaped detection without the use of routine electrocardiographic and enzyme studies. The incidence of late impairment of myocardial function is however sufficiently high to demand careful observation of the operative and postoperative course of each patient in an effort to detect signs of iatrogenic damage and where possible to eliminate the cause Routine recording of electrocardiograms and serum SGOT and LDH levels in the first two postoperative days with further studies in selected cases, should provide useful information for the future CPK estimation provided similar information to SGOT and LDH but in the present series this enzyme showed weaker correlation with electrocardiographic abnormalities and added no significant information

Summary

Electrocardiographic and enzyme studies were made on an unselected series of 172 patients admitted to the intensive care unit after cardiac surgery using cardiopulmonary bypass Fifty eight patients had aortic valve 22 patients multiple valve 40 patients mitral valve 27 patients congenital and 25 patients ischemic disease There were five hospital deaths The following observations were made preoperatively and on the first second and third postoperative days 13 lead electrocardiograms serum glutamic oxaloacetic transaminase lactic dehydrogenase creatine phosphokinase and alkaline phosphatase At least one further electrocardiogram was recorded later in the hospital stay In 88 of the patients isoenzymes of LDH were measured. Details of surgical technique and the postoperative course were recorded in each patient

SGOT and LDH values were elevated in all groups but were highest in patients with aortic and multiple valve disease LDH isoenzyme patterns were typical of myocardial damage in only a small number of patients with high total enzymes There was no relationship between

high enzyme levels and age hemolysis during bypass or postoperative complications but a correlation between enzyme levels and cardiopulmonary bypass time was shown in patients in the aortic and congenital groups and between enzyme levels and aortic cross clamping time in patients in the aortic and mitral groups

Twenty seven out of 34 patients with a peak postoperative SGOT level equal to or greater than 200 units per milliliter showed electrocardiographic evidence of myocardial damage but only nine out of 138 patients with SGOT levels less than 200 units per milliliter showed such evidence All but one patient in the aortic and multiple groups showing myocardial damage had an SGOT level equal to or greater than 200 units per milliliter but SGOT levels in patients in the mitral congenital and ischemic groups showing myocardial damage were usually around 100 units per milliliter Myocardial damage was more common in the aortic multiple and ischemic groups In patients in the aortic group prolonged ventricular fibrillation during operation was associated with high postoperative enzyme levels but this was largely explained by faulty coronary perfusion in some patients

It is concluded that postoperative elevation of serum enzymes is in part an inevitable consequence of cardiopulmonary bypass but exceptionally high levels usually indicate myocardial damage Routine recording of electrocardiograms serum SGOT and serum LDH levels on the first two postoperative days is recommended for all patients

The technical assistance of Miss Alison Buchanan Mr Grant Cathro and staff is gratefully acknowledged. Computer programs for statistical analysis were written by Dr R. M. L. Whitlock. Patients studied with myocardial infarction or myocardial ischemia were under the care of Dr R M Norris.

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Comparison of ventricular parasystole with other dysrhythmias after acute myocardial infarction

R H Baxter MB Ch B MRCP (UK) DCH
J B McGuinness MD FRCP (Glas) MRCP (Lond)
Glasgow Scotland

Continuous monitoring of cardiac rhythm in patients who have had an acute myocardial infarction has added greatly to our knowledge of the disorders of rhythm which can occur in this condition Yet still there are areas where a certain lack of agreement persists particularly in the dysrhythmias arising from the injured left ventricle For example slow idioventricular rhythm is regarded as benign [1] or potentially lethal,[2] depending on one s personal experience In addition ventricular parasystole has been observed in the postinfarction period and been reported as benign [3]

A prospective study was therefore designed to compare our experience in this field of ventricular dysrhythmias with that reported by earlier workers paying particular attention to the so called benign rhythms

Patients and methods

In a sixteen month period, 705 patients were admitted to the coronary care unit (CCU) of the Victoria Infirmary Glasgow In 369 patients (249 males, 120 females) a diagnosis of acute myocardial infarction was made according to World Health Organization criteria.[22] Our unit policy was to admit patients irrespective of age or past history if this diagnosis was suspected and if a bed was available

A 12 lead electrocardiogram (ECG) was recorded in every patient on admission and then daily while in the unit. Continuous monitoring was provided by bedside Sanborn viso monitors

From th Departm nt of Card logy Victoria Infirmary La gside Glasgow Scotla d, U K

Reprint req ests D R. H Baxter V ctoria Infirmary Lang ide Glasgow Scotland, U K

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Table I Analysis of ventricular dysrhythmias after acute myocardial infarction (139 patients) (note some patients had more than one type of dysrhythmia)

	Total	*Death in hospital*
Primary ventricular fibrillation	12	5
Secondary ventricular fibrillation	15	15
Ventricular tachycardia	26	12
Idioventricular rhythm	6	2
Ventricular parasystole	15	–
Ventricular extrasystole	107	32

(Model 780B) linked to centrally placed Lanelec oscilloscopes Thus each patient s cardiac rhythm was constantly visible and when an aberration was observed, a tracing was recorded by the Sanborn unit these strips being subsequently analyzed. When an arrhythmia was prolonged or repetitive a continuous tracing was obtained by an Elema Schonander Minograph 81 ink jet recording the instrument being operated at a slow speed (5 mm per second)

In our analysis of rhythm standard accepted criteria were used.

Ventricular tachycardia was identified as a succession of three or more extrasystoles arising from a single focus in the ventricles and with a rate greater than 100 per minute If the rate with similar complexes was under 100 per minute without P waves a diagnosis of idioventricular rhythm was made but broad complex slow rhythms associated with terminal pump failure were excluded.

Ventricular fibrillation (VF) was regarded as secondary if it occurred in a patient with obvious

Table II Ventricular parasystole

Case No.	Age	Sex	Heart rate per minute	PR interval (sec)	Fusion beats	Variable coupling	Interectopic interval (shortest one)*	Ectopic cycle length* (average)
1	69	M	112	0 12	+	+	120 = 3 × 40	42
2	59	M	100	0 12	+	+	200 = 4 × 50	54
3	64	M	50	0 12	–	+	188 = 5 × 38	40
4	68	M	94	0 14	+	+	220 = 2 × 110	109
5	57	F	88	08	–	+	120 = 3 × 40	41
6	49	M	79	0 16	–	+	400 = 5 × 80	82
7	81	M	88	0 12	+	+	350 = 10 × 35	36
8	63	M	68	0 14	+	+	460 = 15 × 31	33
9	71	F	82	0 12	+	+	128 = 2 × 64	65
10	61	M	68	0 12	+	+	120 = 2 × 60	60
11	64	F	54	A F	+	+	148 = 2 × 74	77
12	68	M	80	A F	+	+	136 = 2 × 68	68
13	49	M	75	0 20	+	+	144 = 2 × 72	74
14	50	M	55	0 20	+	+	260 = 3 × 87	80
15	54	F	80	0 12	+	–	210 = 3 × 70	72

S = survived
Recorded in hundredths of a second.

complications such as shock, hypotension (systolic blood pressure < 100 mm Hg), or cardiac failure,[4 5] but where unexpected with no obvious precipitating factor except the infarction itself it was considered to be primary

Ventricular parasystole was diagnosed according to standard criteria namely the presence of variable coupling, fusion beats[6] and interectopic intervals in simple multiples of one basic revealed or calculated ectopic cycle length [3 7 8]

Treatment

Unless contraindicated patients were anticoagulated with heparin and warfarin Usually sedation was achieved with diazepam and analgesia, when required, by means of diamorphine hydrochloride or dihydrocodeinone bitartrate All received oxygen by plastic (MC) mask for the first 48 hours

Lignocaine was administered when ventricular extrasystoles showed the following characteristics (1) more than five per minute (2) extrasystoles falling on or near the T wave of a normal complex, the so called R on T phenomenon, (3) runs of extrasystoles occurring in salvos of three or more (4) coupled ventricular ectopic beats and (5) multifocal ectopic complexes

Patients with idioventricular rhythm and ventricular parasystole also received Lignocaine A 50 mg bolus was given intravenously followed by continuous infusion in 5 per cent dextrose in a dose sufficient to suppress ectopic activity starting at a rate of 1 mg per minute Ventricular fibrillation and ventricular tachycardia were treated by precordial thump[9 21] followed immediately if necessary, by a 400 Watt second direct current shock and thereafter by Lignocaine infusion

In the absence of any serious complication all patients were kept in the CCU under observation for three days and thereafter transferred to a conventional hospital ward Average hospital stay was three weeks In the event of a complicating dysrhythmia they were kept in the CCU until at least 24 hours after it had completely settled

Results

A diagnosis of acute myocardial infarction was made in 369 patients (249 males 120 females) with a mortality on discharge from the CCU of 70 (19 per cent) which had risen to 90 (24 7 per cent) by the time of discharge from the hospital

Ventricular dysrhythmias were recorded in 139 patients (38 per cent) In this group there were 43 (31 per cent) hospital deaths while in the

Calculated discharge rate per minute	*Manifest discharge rate per minute*	*Site of infarct*	*Outcome*
142	142	Ant	S
112	30	Post.	S
150	150	Post	S
55	55	Post	S
146	146	Post	S
73	15	Post	S
166	16	Ant	S
181	14	SGOT	S
92	92	Ant	S
100	100	Ant	S
78	78	Ant	S
88	88	SGOT	S
80	80	Ant	S
72	72	Post	S
75	75	Post	S

remaining 230 patients with no record of ventricular dysrhythmia there were 48 deaths (21 per cent) Detailed analysis is shown in Table I

Twenty seven (7 3 per cent) patients developed ventricular fibrillation Twelve were regarded as primary although two of these presented as car diac arrests in the Admissions Department and may well have had shock or failure prior to ar rival in hospital Primary VF was preceded by frequent ventricular extrasystoles in at least four patients and by ventricular tachycardia in six pa tients

Secondary or complicating VF occurred in 15 patients of whom 14 had cardiogenic shock and four acute left ventricular failure These episodes of VF were preceded by frequent ventricular ex trasystoles in nine patients and ventricular tachycardia in nine patients. Of the 27 patients with VF only seven (26 per cent) survived to leave the hospital and all of these had primary ven tricular fibrillation

Episodes of ventricular tachycardia occurred in 26 patients (7 per cent) In 17 patients, earlier ventricular extrasystoles were recorded and these occurred frequently (more than 5 per minute) in 16 patients but the remaining 9 pa tients had no identified prior ectopic activity

Twelve patients died a mortality of 46 per cent which seemed independent of the presence or ap parent absence of preceding ventricular ex trasystoles However when VF complicated the ventricular tachycardia (15 patients) there were 10 deaths (67 per cent) compared to only two deaths (18 per cent) in the remaining 11 patients One patient with ventricular tachycardia had Wolff Parkinson White syndrome still present at follow up three months later

Idioventricular rhythm was recorded in only six patients. Clinically there was no gross hemodynamic upset and the rhythm settled satisfactorily In no instance was ventricular fibrillation recorded, but two of these patients died during convalescence one from persistent left ventricular failure and one suddenly from further myocardial infarction

Ventricular parasystole was identified in 15 patients (4 1 per cent) (11 males and 4 females) In six patients the site of infarction was anterior in seven patients it was posterior while two pa tients had transaminase rises alone Further details are shown in Table II Variable coupling was present in all cases except Case 15 in this in stance the revealed ectopic discharge rate was very similar to the sinus rate but the presence of fusion beats indicated the true parasystolic nature of the rhythm Fusion beats were seen in all but three patients. Their presence is not es sential for a diagnosis of a parasystolic focus[6] in the presence of undoubted variable coupling and interectopic intervals in multiples of the basic ec topic cycle length

In most cases the parasystolic beats appeared intermittently indicating a degree of exit block but in 11 instances the ectopic cycle length was revealed at some time (Fig 1) indicating varia tion of the block However some patients pre sented with episodes of continuous ectopic rhythm rather like a slow ventricular rhythm but its parasystolic nature was revealed by measurement of the intervals between episodes of ectopic rhythm which were in multiples of the ectopic cycle length (Fig 2) in addition fusion beats were present particularly at the start of an episode of the ectopic rhythm (Fig 3) The calcu lated parasystolic rates were usually over 70 per minute

All patients received Lignocaine and none de veloped ventricular tachycardia or fibrillation

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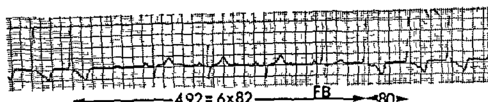


Fig 3 Shows episodes of sinus rhythm alternating with episodes of ectopic ventricular rhythm The interval between the episodes of ectopic rhythm is an exact multiple of the basic ectopic cycle length This and the presence of the fusion beat (FB) indicates the parasystolic basis of the rhythm (Case 14)

Table III Analysis of ventricular extrasystole in 107 patients showing the frequency of complication by VT and VF and subsequent mortality

	Total	Complicated by ventricular tachycardia	Complicated by ventricular fibrillation
Ventricular extrasystoles Rate > 5/min	87 (25)	16 (8)	13 (11)
Ventricular extrasystoles Rate < 5/min	20 (7)	1 (0)	1 (0)
Ventricular extrasystoles with R/T phenomenon	6 (2)	4 (2)	4 (2)
Multifocal ventricular extrasystoles	16 (10)	7 (5)	8 (6)

Numbers parenth ses indi te numbe s of d ths

awareness of the observer Our incidence in the present series was 4 1 per cent We regard it as important to record long strips of ECG when extrasystoles occur as this draws attention to the various features of the rhythm Parasystole has been reported in normal people [14] but is very rare in the absence of organic heart disease [6 23] It has been produced experimentally [15] Clinical accounts are infrequent particularly in reports of ventricular dysrhythmias after acute myocardial infarction In a report of 105 cases of parasystole Chung[14] recorded evidence of hypertension or arteriosclerotic heart disease in 57 per cent but only 7 6 per cent (8 patients) had acute myocardial infarction In another report [16] of 11 patients with parasystolic tachycardia, three patients had acute myocardial infarction More recently Salazar and McKendrick[3] reported 11 cases in a study of parasystole after acute myocardial infarction and commented on the apparent benign nature of the rhythm a view which the present study supports However the presence of ventricular extrasystoles after acute myocardial infarction has been well documented,[10 12 17] and the incidence here of 30 per cent and a mortality of 27 per cent is similar to other reported series using this type of monitoring [2 11] The importance of ventricular extrasystoles which are either frequent multifocal in origin or show the R on T phenomenon is in their tendency to precede more serious ventricular tachyarrhythmias [18] This was confirmed in this study but it was also noted as it has been by others [4 19] that a significant number of patients who developed ventricular tachycardia or ventricular fibrillation had no preceding ectopic activity There was a higher mortality among patients with infrequent ectopic activity than in those with frequent extrasystoles review of the causes of death in the former showed that in no case was the death attributable to a tachyarrhythmia and of course those found to have frequent ectopic beats were treated with intravenous Lignocaine It is interesting to note that even before the days of monitoring the identification of ventricular ectopic beats on routine ECG tracing was recognized as an adverse prognostic factor in acute myocardial infarction [20]

In contrast the absence of any mortality among the patients with ventricular parasystole lends support to the view that this is a benign rhythm and the absence of progression to ventricular tachycardia or ventricular fibrillation may be due to the presence of exit block in

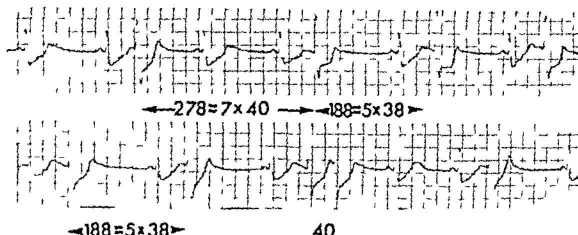


Fig 1 In the top tracing there is a small variation in the coupling interval (> 0 08 sec) but the lower tracing (from the same patient—Case 3) shows not only a larger coupling interval but the interectopic intervals are in direct multiples of the basic cycle length which is revealed in complexes 6 and 7

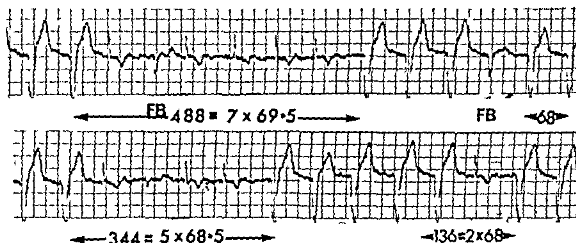


Fig 2 Shows the continuous tracing from a patient (Case 12) with atrial fibrillation and episodes of continuous ectopic rhythm Fusion beats (FB) are seen and the intervals between the episodes of continuous ectopic rhythm are in multiples of the basic ectopic cycle length indicating a parasystolic basis to the ectopic rhythm

One patient (Case 11) was on digoxin All survived.

Ventricular extrasystoles were seen in 107 patients (Table III) Of these 32 patients (30 per cent) died in hospital compared to 48 deaths (21 per cent) in those patients who showed no evidence of ventricular dysrhythmia (230 patients) Where the frequency of the ventricular extrasystoles was less than 5 per minute, the mortality was 35 per cent compared to 28 per cent in those with more than 5 per minute Only six patients had ventricular extrasystoles with the 'R on T wave" phenomenon but four of these developed VT and VF and two died Sixteen patients had extrasystoles with multifocal origin and nine of these had at least one episode of VT or VF or both

Discussion

Ventricular fibrillation is observed in about 10 per cent of hospital patients with acute myocardial infarction[2, 10] and 10 to 25 per cent have episodes of ventricular tachycardia[11, 12] Idioventricular rhythm not associated with terminal states has been variously reported as occurring in 8 to 30 per cent[1, 13] The incidences in the present series were VF, 7 3 per cent VT, 7 0 per cent, and idioventricular rhythm in under 2 per cent It seems likely that differences in the incidence of dysrhythmias from different units may be due in part to different methods and intensities of cardiac monitoring

Ventricular parasystole is regarded as a rare rhythm although Friedberg[7] has suggested that the frequency of detection is partly related to the

Experimental and laboratory reports

Effect of E-electrode position on Frank vectorcardiogram in children

Barbara Guller MD
Craig Reeves*
Ralph E Smith MD
Rochester Minn.

In studies of the applicability of the Frank lead system to infants and children Gamboa and Gersony[1] found from torso models that with younger ages, accurate placement of electrodes is increasingly important This is a report of the effect of the displacement of the E electrode on the Frank vectorcardiogram in 50 children whose ages ranged from birth to 15 years

Material and methods

In 26 children less than 3 years old and in 24 who were between 3 and 15 years old three Frank vectorcardiograms were recorded on line with the Mayo Clinic computerized system[2] with the E electrode in the ideal position (midline) shifted ½ inch to the right and shifted ½ inch to the left There were 10 children in each of the following 5 age groups 1 to 10 days 1 to 12 months 1 to 5 years 5 to 10 years and 10 to 15 years The amount of displacement of the E electrode was the same in all age groups making results of this study comparable to those of Gamboa and Gersony[1] in which the E electrode was displaced to the same extent in torso models representing various ages All precordial electrodes of the Frank system were placed at the height of the fifth intercostal space with the child supine[2,3] Scalar electrocardiograms were recorded simultaneously with all vectorcardiograms and were reviewed to ensure that no changes in electric potential independent of the E electrode displacement occurred In every child the transverse external diameter of the thorax at the height of the fifth intercostal space was measured either directly from the chest or indirectly from the chest roentgenogram

The following vectorcardiographic parameters were evaluated

1 The amplitudes of R and S waves in Leads Z and X with the amplitudes measured by hand from tracings of these leads that had been plotted on line by a digital to analog plotter

2 Angles and magnitudes of the following vectors of the Mayo Clinic computer output matrix[2,3] maximal instantaneous QRS vector (RMAX) mean QRS vector (RR) mean vector over the initial 30 ms (ROR3) and the mean vector over the terminal 40 ms (RER4) The differences in amplitudes of the R and S waves occurring in Leads X and Z with displacement of the E electrode and differences in magnitudes of the selected vectors of the computer matrix were expressed as percentage of the magnitude seen with the E electrode in the ideal position because there is an inverse relationship between body surface potentials and the size of the thorax in children[1]—a relationship that might make the changes in the younger age groups appear to be larger Differences in angles of selected vectors were termed positive when they occurred in a counterclockwise direction and negative when they occurred in a clockwise direction[3]

Results

Leads X and Z Changes due to the modified position of the E-electrode on amplitudes of the R and S waves were pronounced in Lead Z and of

From the Mayo Clinic and Mayo Foundation, Rochester Minn

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Reprint requests Dr B Guller c/o Section of Publications Mayo Clinic, 200 First St SW Rochester Minn. 55901

*Mr Reeves was a premedical student at the time this study was done

parasystolic rhythms[7] Parasystolic rhythms were treated as part of our general policy toward ectopic rhythms and in agreement with others[3] the rhythm settled quickly and there were no complications from anti arrhythmic therapy with Lignocaine However, it does not seem to be a fatal dysrhythmia after acute myocardial infarction as in other situations and treatment may be unnecessary[14]

Summary

Three hundred and sixty nine patients suffering from a recent myocardial infarction were studied over a period of 16 months in a coronary care unit Particular attention was paid to ventricular arrhythmias and especially ventricular parasystole Ventricular parasystole was found in 4 per cent of the patients identification being helped by the recording of long strips of ECG at slow speed when ventricular ectopic activity was noted.

The study has shown that ventricular parasystolic rhythms after acute myocardial infarction are probably benign in contrast to most other ventricular arrhythmias which are associated with an increased mortality

We wish to thank the Consultants in the Medical Division of the Victoria Infirmary whose patients were studied, Dr T Semple for helpful criticism and advice Sister K Scott and *staff in the coronary care unit, and the many house physicians* who helped to collect the tracings

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Table I Effects of E electrode position on Frank vectorcardiogram in children

Age	E electrode shift	No. of children	Percentage change in Lead X		Percentage change in Lead Z		Percentage change in magnitude of spatial vectors*			
			R wave	S-wave	R wave	S-wave	Maximal QRS vector	Mean QRS vector	Initial mean 30 ms. vector	Terminal mean 40 ms. vector
<3 yr	Right	26	0 0 (−32 0)	0 2 (24 7)	−18 3 (8 9)	−23 7 (27 9)	−5 8 (11 9)	12 5 (38 3)	5 8 (77 1)	6 8 (20 8)
	Left	26	−1 8 (19 9)	1 5 (32 7)	5 9 (16 5)	28 0 (68 1)	2 8 (15 8)	15 0 (54 7)	30 6 (106 2)	6 5 (36 9)
≥3 yr	Right	24	0 3 (9 7)	4 9 (26 7)	−14 5 (12.2)	−9 7 (12 8)	−1 4 (8.2)	−1 0 (15 5)	2 3 (51 1)	−2 7 (29 7)
	Left	24	−0 4 (11 4)	0 0 (17 4)	3 9 (15.3)	−0 7 (27 8)	1 3 (9 6)	3 5 (19 4)	10 6 (32 7)	5 6 (27 2)

Ch nges occurring with E-electrode in modified position (right o left) are exp essed as percentag of magn tude measured with E electrode in id al po tion. N mbers in uppe line are mean values numbers in lower line in parenth s are standard deviations

Table II Voltage amplitudes of R and S waves in Lead V_1 while E lead was shifted

Age	E-electrode shift	No of children	Percentage change in Lead V_1*	
			R wave	S wave
<3 yr	Right	26	4 3 (19 6)	−1 9 (18 6)
	Left	26	4 5 (18 9)	−0 4 (8 3)
≥ 3 yr	Right	24	0 7 (10 1)	−2 5 (66)
	Left	24	0 2 (8 3)	−2 6 (22 1)

Lead V_1 remained in a fixed position while Le d E was shifted. Chang taking place in Lead V_1 with E-electrode n modifi d pos tion (right or left) are expressed as percentage of magnitud with E-electrode in id l positi n. Numbers in upper line are mean valu s numbers in lower line in pare theses are standard deviations.

E-electrode could not be reliably predicted In children who were 3 years old or older a slight decrease in amplitude occurred with rightward displacement of the E electrode in the maximal mean and terminal 40 ms vectors while left ward displacement of the electrode caused a slight increase in the amplitude of these seg ments (Fig 3)

Frontal and horizontal planes (Table III) The changes dependent on E electrode position af fecting vector magnitudes and vector directions of selected parameters of the QRS loop were larger in both planes in children less than 3 years of age than in those who were older for most of the subjects. Rightward or leftward displacement of the E electrode did not produce a consistent in crease or decrease of these selected vectorcar diographic parameters in both age groups (Figs 4 and 5)

Discussion

The effect of a lateral shift of the E electrode to the right or to the left on the Frank QRS vector loop configuration was more pronounced in children who were less than 3 years of age than in older children While the displacement caused only minor changes in the configuration of the frontal plane loop the horizontal plane loop con figuration was considerably altered and tended to show a reduction in its anteroposterior diameter with a rightward shift of the E electrode and an increase in its anteroposterior diameter with a

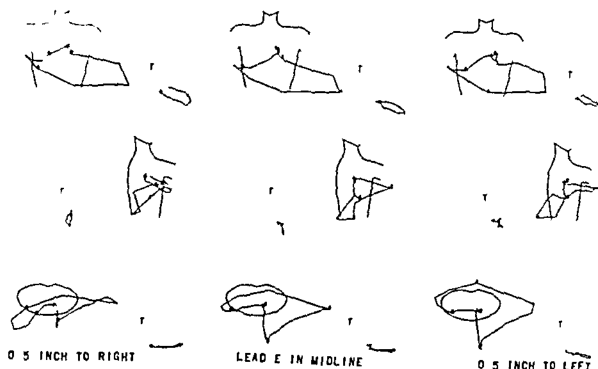


Fig 1 Effect of E electrode position on Frank vectorcardiogram in 22 month-old infant

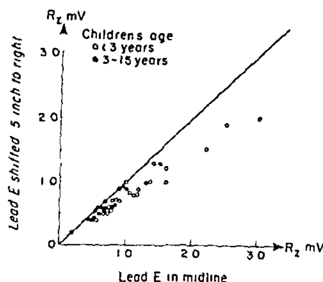


Fig 2 Effect of rightward shift of E electrode on R wave voltage amplitude of Lead Z

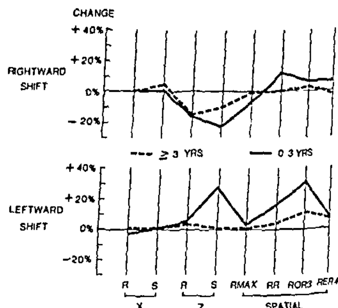


Fig 3 Changes of voltage amplitudes in Leads X and Z and of *spatial magnitudes of selected vectors of QRS complex* Means of changes are expressed as percentage of values *measured with E electrode in ideal position.*

little significance in Lead X (Table I) Rightward displacement of the E electrode resulted in a decrease of the amplitudes of R and S waves in Lead Z while leftward displacement tended to increase these amplitudes (Figs 1, 2, and 3) Effects were more pronounced in children who were less than 3 years old than in those 3 years old or older Mean values of changes in R and S wave amplitudes in Lead Z were considerably larger than mean values of changes in simultaneous amplitudes of R and S waves in Lead V_1 (Table II), a lead that remained in fixed position while the E electrode was shifted There was no relationship between the amount of E electrode displacement expressed as a percentage of chest diameter and changes in voltages in Leads X and Z With displacement of the E electrode of as low as 7 per cent of chest diameter a change in recorded potentials of 70 per cent was observed.

Spatial magnitudes (Table I) *In children less* than 3 years of age because the standard deviations for changes of selected vector segments (initial 30 ms, mean QRS, maximal QRS and terminal 40 ms) were large the expected shifts with a rightward or leftward displacement of the

a 70 per cent change in amplitude of recorded potentials (sum of R and S waves in Lead Z) thus inaccuracy of positioning the E electrode in pediatric patients who for example undergo a midline thoracotomy may significantly alter the horizontal vector loop

Results of this study confirm the prediction of Gamboa and Gersony[1] from torso models that with younger age groups the effect of lateral displacement of Frank electrodes is more pronounced. Nevertheless Gamboa and Gersony found that equal lead response of the Frank system was present to the same extent in torso models of the newborn as in those of the adult

In the original description of his vectorcardiographic system Frank pointed out that the omitting or displacing of electrodes contributing to the X Y and Z leads results in increased sensitivity to a shift of the dipole location within the heart.[4] Recent studies on surface potential maps in children by Blumenschein and co workers[5] suggest that during the QRS cycle dipole projection onto the thorax results in a crowding and near vertical course of isopotential lines in the region of the E electrode when maximal voltages along the Z axis are recorded which might explain the effect of the E electrode shift on amplitudes of R and S waves in Lead Z

Among the electrodes contributing to the negative pole of the Frank Lead Z electrode E has the greatest weight[4] and, therefore it might be expected to be most sensitive to a dipole shift however Gamboa and Gersony[1] demonstrated that the correct position of electrode C which also contributes to the negative pole of Lead Z and which is affected by proximity effects may be more crucial than that of the E electrode

Summary

In 50 children whose ages ranged from birth to 15 years the effect of E electrode position on the Frank vectorcardiogram was tested A rightward shift of this electrode by 0 5 inch resulted in a decrease in the anteroposterior diameter of the horizontal vector loop whereas a leftward shift of 0 5 inch tended to increase this dimension Effects of E lead displacement were less marked in children who were 3 years old or older than in those who were younger—the accurate placement of the E electrode was crucial in the younger group

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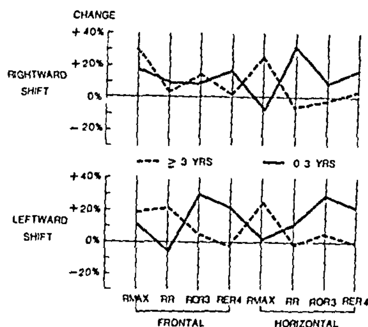


Fig 4 Directional changes in degrees for selected vectors of QRS complex

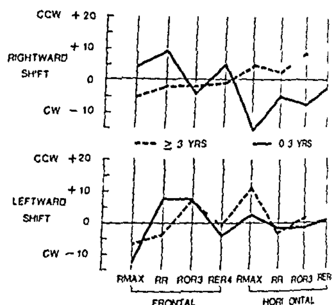


Fig 5 Changes of voltage amplitudes of selected vectors of QRS complex Means of changes are expressed as percentage of values measured with E electrode in ideal position.

Table III Effects of E electrode position on selected parameters in frontal and horizontal Frank vectorcardiogram of children

Age	E electrode shift	Parameter	No of children	Percentage change in frontal vectors*				Percentage change in horizontal vectors*			
				Maximal QRS	Mean QRS	Initial mean 30 ms.	Terminal mean 40 ms.	Maximal QRS	Mean QRS	Initial mean 30 ms	Terminal mean 40 ms.
< 3 yr	Right	Angle†	25	4 0	8 8	−5 0	4 8	−16 4	−4 7	−7 5	−2 5
				(41 0)	(22 0)	(57 3)	(15 7)	(41 7)	(15 8)	(18 4)	(17 9)
		Magnitude	25	18 0	9 1	9 4	16 9	−7 1	32 3	9 4	16 9
				(46 8)	(54 1)	(83 1)	(38 4)	(34 9)	(70 5)	(83 1)	(38 4)
	Left	Angle†	25	−14 0	7 1	6 7	−4 5	2 6	−1 8	−1 6	0 4
				(39 3)	(39 4)	(50 8)	(30 0)	(77 6)	(19 9)	(15 8)	(21 7)
		Magnitude	25	11 1	−5 8	28 7	21 9	2 0	10 7	28 7	21 9
				(53 7)	(39 0)	(74 1)	(39 9)	(38 0)	(47 3)	(74 1)	(39 9)
≥ 3 yr	Right	Angle†	22	−5 4	−2 0	−1 8	−1 3	5 3	2 4	8 3	5 0
				(25 4)	(32 5)	(7 4)	(8 7)	(35 0)	(19 0)	(27 4)	(19 1)
		Magnitude	22	31 3	3 0	14 5	2 2	25 9	−6 2	−2 6	3 9
				(70 6)	(34 1)	(53 7)	(26 3)	(95 0)	(30 0)	(11 1)	(39 1)
	Left	Angle†	22	−6 8	−4 4	7 2	−0 6	10 7	−3 5	1 9	4 5
				(29 7)	(24 5)	(28 5)	(8 9)	(34 2)	(34 2)	(33 7)	(12 2)
		Magnitude	22	18 6	22 5	3 8	−0 7	26 3	−1 4	4 8	−1 3
				(85 6)	(102 0)	(16 2)	(19 8)	(83 6)	(21 3)	(14 0)	(16 8)

Changes occurring with E electrode in modified position (right or left) are expressed as percentage of magnitude measured with E electrode in ideal position Numbers in the upper line are mean values numbers in lower line in parentheses are standard deviations
†When changes in angles occurred in counterclockwise direction they were termed positive and when they occurred in a clockwise direction they were termed negative"

leftward shift (Figs 1 and 2) The effects of the E electrode shift on the magnitude of R and S waves of Leads Z and X were more predictable than on selected vectorcardiographic parameters of the frontal and horizontal vector loop (angles and magnitudes of initial terminal mean and maximal QRS vectors) presumably because of a wide variation in the direction of these selected variables with Lead E in the ideal position Inaccuracy of E electrode displacement amounting to 7 per cent of the transverse thoracic diameter at the level of the E electrode resulted in as much as

Table I Clinical data

Patient	Sex	Age (years)	Surface area (M²)	Cause of myocardial disease	Heart rhythm	Clinical class (NYHA)	Digitalis	Diuretic
1	M	46	1 89	Unknown	S	II	No	No
2	M	42	1 90	Alcohol	S	III	Yes	Yes
3	M	50	1 85	Unknown	S	I	Yes	Yes
4	M	56	1 86	Unknown	S	II	Yes	Yes
5	M	45	1 77	Alcohol	S	III	Yes	Yes
6	M	56	1 74	Unknown	S	I	Yes	No
7	M	61	1 93	Lymphosarcoma radiation	S	II	Yes	Yes
8	F	52	1 56	Unknown	S	I	Yes	Yes
9	M	30	1 95	Familial	S	II	Yes	Yes
10	M	35	1 88	Unknown	J	I	Yes	No
11	M	56	1 63	Viral myocarditis ?	S	I	Yes	Yes
12	M	18	1 85	Viral myocarditis ?	S	II	Yes	No
13	M	53	1 85	Unknown	S	II	Yes	Yes
14	F	62	1 40	Unknown	S	II	Yes	Yes
15	M	50	1 73	Unknown	S	II	Yes	Yes
16	M	53	1 95	Unknown	F	I	Yes	Yes
17	M	63	1 81	Unknown	S	III	Yes	Yes
18	F	37	1 57	Viral myocarditis ?	S	I	Yes	Yes
19	M	54	2 08	Unknown	S	II	Yes	Yes
20	M	54	1 93	Unknown	S	II	Yes	Yes
21	M	44	1 93	Unknown	S	III	Yes	Yes
22	M	50	2 30	Unknown	F	II	Yes	Yes
23	M	57	2 00	Unknown	F	I	Yes	Yes
24	M	46	1 80	Alcohol	S	II	Yes	Yes
25	F	55	1 70	Unknown	S	II	Yes	Yes
Mean		49 0	1 83					
1 S.D		10 4	0 18					

Symbols F atrial fibrillation S sinus rhythm and J junctional rhythm.

corder Details of the technique of patient examination have been previously described.[7] In summary the study was performed with the patient semi recumbent and the thorax rotated into the right anterior oblique posture The transducer was placed in the third or fourth left intercostal space near the left sternal edge and the heart systematically scanned by altering the direction of the ultrasound beam until echoes from the mitral valve left ventricle and aorta had been identified. The echoes from the mitral valve and the wave form of the left ventricular echoes were then used as guides to ensure a reproducible direction of the ultrasound beam across the chamber when recording for quantitative studies No recording of the echocardiographic left ventricular dimension was accepted as valid unless echoes from the internal surface of the left ventricle (the left side of the interventricular septum and endocardial surface of the posterior left ventricular wall) had been recorded simultaneously The reproducibility of measurements made in this way had been established.[5,7] Since the amplitude of motion of the left ventricular wall is reduced in patients with myocardial disease particular care was taken not to mistake the outer surface of the left ventricular walls (right side of the interventricular septum and epicardial surface of the posterior left ventricular wall) for the inner surface Such an error suggests a spuriously large left ventricular cavity and more severe impairment of wall motion

An example of a left ventricular echocardio

Model DR 8 Electronics for Medicine White Plains N Y

A comparison of the relative value of noninvasive techniques—echocardiography, systolic time intervals, and apexcardiography—in the diagnosis of primary myocardial disease

Ian G McDonald, M D, F R A C P
Edison R Hobson, M B, Ch B, M R A C P
Fitzroy Australia

The clinical diagnosis of primary myocardial disease is still usually made by exclusion when the evidence obtained from the history, physical examination, electrocardiogram, and chest x ray suggests myocardial hypertrophy or damage which cannot be reasonably attributed to mechanical overload of cardiac chambers nor to ischemic heart disease Confirmation of the diagnosis by cardiac catheterization is generally reserved for those patients in whom diagnostic doubt remains particularly if there is any suspicion of a correctable lesion such as occult valve disease or ischemic left ventricular damage which could be amenable to surgery Noninvasive methods of established value in the detection of impaired myocardial function are the apexcardiogram[1,2] and measurements of systolic time intervals [3] The more recent application of echocardiography to assessment of left ventricular size and function[4-8] has offered an alternative and direct method of obtaining a quantitative assessment of myocardial function Our aim has been to assess the respective merits of these noninvasive techniques in clinical practice

Methods

Patients studied Echocardiography was attempted in 28 patients with primary myocardial

From the Cardiovascular Diagnostic Unit St Vincent s Hospital Melbourne Australia
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Reprint requests to Dr Ian McDonald Director Cardiovascular Diagnostic Unit St Vincent s Hospital Victoria Parade Fitzroy 3065 Australia

disease in six of whom the diagnosis was confirmed by cardiac catheterization with left ventricular cineangiography and selective coronary angiography Patients with hypertrophic subaortic stenosis were specifically excluded In three of these patients the left ventricular echoes were considered technically unsatisfactory (see below) Phonocardiography and apexcardiography were performed on the remaining 25 patients whose relative clinical details have been summarized in Table I Their symptoms were graded according to the functional classification of the New York Heart Association [9] The patients with primary myocardial disease were divided into two groups for further analysis Eight patients without dyspnea (Class I) formed one group while the remaining 17 patients with dyspnea (Classes II or III) comprised the other group

Control values for the ultrasound measurements and for systolic time intervals were available for 25 healthy subjects with no cardiovascular abnormality on clinical examination or chest roentgenogram Since apexcardiography had not been performed in this series the normal values for this investigation were established separately for 25 normal volunteer subjects selected in a similar manner, in whom technically satisfactory apexcardiograms had been obtained

Technique Echocardiography was performed with a 1 27 cm, 2 25 mHz transducer* and a standard echoscope † M mode recordings were made by polaroid photography of the oscilloscope screen or on a multichannel oscilloscopic re

*Smith Kline Instruments Palo Alto Calif
†Ekoline 20 Smith Kline Instruments Palo Alto Calif

Weissler Harris and Schoenfeld [13] recording heart sounds from microphones at the cardiac apex and second left intercostal space together with the electrocardiogram and indirect carotid pulse tracing The latter was recorded by a hemispherical capsule (diameter 2 cm) connected to a gas transducer* by a short length of rubber tubing Respiration was monitored by a variable resistance gauge The ratio of the pre ejection period (PEP) to the left ventricular ejection time (LVET) was calculated and used as an index of left ventricular function [13]

Apexcardiography was performed using the same recording capsule The air pressure within the capsule was regulated by the operator s finger which controlled an air vent at the apex of the capsule The subject was placed in the right anterior oblique posture and the position of the capsule was carefully adjusted over the apical impulse so as to record the maximum amplitude of the systolic wave and to obtain as clear an atrial wave as possible Attempts were made to improve unsatisfactory recordings by modifying the transducer position patient posture or by recording during the most favorable phase of respiration The amplitude of the atrial wave (A) and of the left ventricular wave from beginning to peak (LV) were measured from the recording and their ratio (A/LV) was calculated.[14] The contour of the systolic wave was also classified as normal or sustained according to the criteria of Sutton Prewitt and Craige [15] The degree of cardiomegaly in the chest roentgenogram was expressed as the cardiothoracic ratio [16]

All of these studies were performed as part of a routine clinical assessment so that no attempt was made to ensure either fasting of the patient or performance of the test at a particular time of day

Results

Echocardiography (Table II) For normal subjects the end diastolic left ventricular dimension (D_d) was $\overline{4\ 43}$ and shortened by 35 3 per cent (FS) at a rate of 1 22 lengths per second (FRS) The end diastolic left ventricular wall thickness (W_d) was $\overline{0\ 91}$ cm and thickened by 66 0 per cent during systolic contraction In patients with myocardial disease the left ventricle was larger and contraction was markedly reduced. Thus D_d was $\overline{6\ 85}$ cm FS $\overline{12\ 2}$ per cent and FRS $\overline{0\ 56}$ lengths per second The difference in values between these two groups of subjects are highly significant Furthermore there was no overlap between the range of values in normal subjects for D_d (3 80 to 5 00 cm) FS (30 4 to 43 9 per cent) and FRS (1 03 to 1 50 lengths per second) and values obtained in patients with myocardial disease (5 80 to 8 05 cm 4 7 to 19 3 per cent and 0 31 to 0 98 lengths per second, respectively) W_d was significantly greater in patients with myocardial disease ($\overline{1\ 11}$ cm) than for normal subjects (0 91 cm) but there was much overlap for this measurement Symptomatic (Classes II and III) patients with myocardial disease had a significantly larger D_d ($\overline{7\ 16}$ cm) than asymptomatic (Class I) patients ($\overline{6\ 18}$ cm) but the differences in FS FRS and W_d were not statistically significant Class I patients showed significant differences from normal in D_d FS FRS and W_d

The technical failure rate for echocardiography was 10 7 per cent and was attributable to failure to record a satisfactory left septal echo in one patient and failure to record either left septal or posterior wall endocardial echoes adequately in two patients

Systolic time intervals The difference in PEP/LVET between normal subjects ($\overline{0\ 325}$) and patients with myocardial disease ($\overline{0\ 621}$) was highly significant and there was no overlap of values The difference between Class I ($\overline{0\ 588}$) and Classes II or III patients ($\overline{0\ 639}$) was not significant but the larger difference between Class I patients and normal subjects ($\overline{0\ 325}$) was statistically significant The correlation between FS and PEP/LVET for normal subjects and patients with myocardial disease was close (r = 0 91) and the discrimination between normal subjects and patients with myocardial disease was enhanced by combining these measurements in the form of a graph (Fig 4)

There was no instance of failure to obtain a recording technically suitable for analysis however in three patients (12 per cent) the presence of left bundle branch block prevented the use of the PEP/LVET ratio as an index of myocardial function

Apexcardiography The A/LV ratio was greater in patients with myocardial disease ($\overline{19\ 7}$ per cent) than in normal subjects ($\overline{9\ 6}$ per cent) The difference between Class I patients and normal

* Sanborn, Model 270

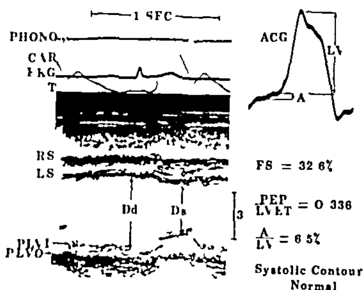


Fig 1 Left ventricular echocardiogram in a normal subject showing echoes from the transducer face T from the inter ventricular septum—right side RS and left side LS and from the posterior left ventricular wall endocardial surface (PLVI) and epicardial surface (PLVO) End diastolic (D_d) and end systolic (D_s) dimensions are indicated The phonocardiogram (PHONO) indirect carotid pulse (CAR) and electrocar diogram (ECG) were recorded simultaneously To the right is the apexcardiogram illustrating the atrial (A) and left ventricular systolic (LV) waves Indices of myocardial func tion from noninvasive investigations have also been sum marized (figures apply to average values not those of the single heart beat illustrated—see text for abbreviations)

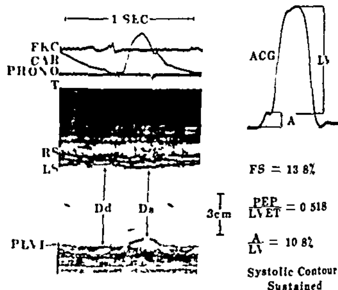


Fig 2 Left ventricular echocardiogram apexcardiogram and derived indices for a Class I patient with myocardial dis ease

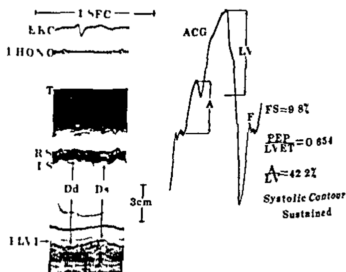


Fig 3 Left ventricular echocardiogram apexcardiogram and derived indices for a Class II patient with myocardial disease

gram in a normal subject is shown in Fig 1 and in patients with myocardial disease in Figs 2 and 3 Myocardial function was assessed by calculat ing *indices of the extent and rate of shortening of* unit length of myocardium [7] Since left ventricu lar contraction is approximately symmetrical about the long axis of the chamber [10 11] contrac tion of the internal minor axis which is approxi mated by the left ventricular echocardiographic dimension[5] reflects proportional changes in the internal circumference *Shortening of this* dimension from end diastole (D_d) to end systole (D_s) was termed total systolic shortening (ΔD_t) Fractional shortening (FS) was then calculated by expressing ΔD_t as a fraction of D_d

$$FS = \Delta D_t / D_d \times 100\ (\%)$$

The dimension at the *onset of ejection* (D_e) was obtained by correcting the upstroke of the in direct carotid pulse tracing for pulse transmis sion time and system delay Shortening during ejection (ΔD_e), the difference between D_e and D was then expressed as a fraction of the initial length D_d and divided by the ejection time derived from the indirect carotid pulse tracing (LVET) to derive a mean fractional rate of shor tening (FRS)

$$FRS = \frac{\Delta D_e / D_d}{LVET}\ (lengths/sec)$$

Left ventricular wall thickness was measured at *end diastole* (W_d) and end systole (W_s) using the method of Feigenbaum and co workers [12]

Phonocardiography was performed in the supine posture immediately after the left ven tricular echoes had been recorded *Systolic time* intervals were measured by the method of

subjects was also significant but there was much overlap between these two groups The difference between Class I ($\overline{17\ 2}$ per cent) and Classes II and III patients ($\overline{20\ 9}$ per cent) was not significant. The systolic contour of the apexcardiogram was abnormal in 14 out of the 18 patients in whom it could be assessed this included five out of six patients in Class I and 9 out of 12 patients in Classes II or III An abnormality of the A/LV ratio or systolic contour was found in 88 9 per cent of the patients with myocardial disease An abnormal diastolic filling wave was also noted in six out of 19 patients all of whom were in severe heart failure but this was never an isolated finding

It was possible to calculate the A/LV ratio in only 13 (52 per cent) of patients with myocardial disease A recording suitable for analysis could not be obtained in seven patients (28 per cent) The reason was inability to feel the apical impulse in four patients (16 per cent) and because of poor quality of the recording of the systolic wave in three patients (12 per cent) There were also two patients in sinus rhythm in whom the recording of the atrial wave was unsatisfactory for calculation of the A/LV ratio and four patients in whom this ratio could not be calculated because of an abnormal heart rhythm—in three patients because of atrial fibrillation and in one patient because of a junctional rhythm The systolic contour of the apexcardiogram could be analyzed in 18 (72 per cent) of the patients

Chest roentgenogram The cardiothoracic ratio was greater for patients with myocardial disease ($\overline{0\ 53}$) and for Class I patients only ($\overline{0\ 49}$) than in the normal subjects ($\overline{0\ 44}$) However there was much overlap between the values in patients with myocardial disease and the normal range particularly for Class I patients This ratio was also significantly smaller for Class I patients than for those in Classes II and III

Discussion

We can evaluate the assessment of left ventricular myocardial function by echocardiography systolic time intervals, and apexcardiography by comparing the ability of these techniques to detect abnormal left ventricular function the physiologic interpretation of an abnormal result, and the technical difficulty of the examination When considering the ability of these tests to discriminate between normal subjects and patients with primary myocardial disease the effects of case selection in this study must be born in mind The clinical diagnosis of primary myocardial disease is usually made only when left ventricular hypertrophy or impairment of left ventricular function is relatively advanced, a fact which will aid its detection by any investigative technique Hence it was not the aim of this study to establish the sensitivity of the noninvasive tests in the detection of impaired myocardial function This will ultimately be established only when these investigations are compared with a test of proved ability to detect impaired myocardial function and which is both sensitive and quantitative Such a test would also need to be suitable for population screening so that asymptomatic sub

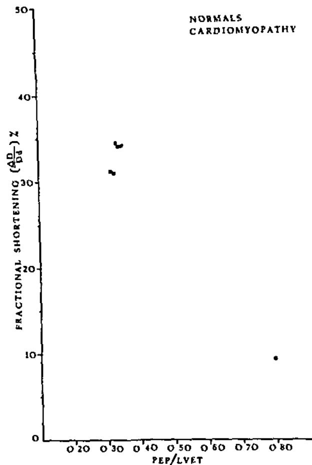


Fig 4 The relationship between fractional shortening of the ultrasonic left ventricular dimension and the PEP/LVET ratio measured from the phonocardiogram in 25 normal subjects and 22 patients with myocardial disease (r = 0 91)

Table II Technical data—myocardial disease

Patient	D_d (cm.)	D_s (cm.)	FS (%)	FRS (lengths/sec.)	W_d (cm.)	W_s (cm.)	PEP/LVET	R R (msec.)	A/LV (%)	Quality of ACG	Systolic contour	Cardiothoracic ratio (%)
1	6.40	6.10	4.7	0.23	0.75	0.80	0.639	520	—	A	S	0.50
2	7.20	6.50	9.8	0.52	1.50	2.00	0.645	640	42.2	T	N	0.51
3	6.70	5.90	11.9	0.59	1.20	1.50	0.563	770	26.7	T	S	0.48
4	7.70	6.90	10.4	0.34	1.30	1.80	LB	750	—	L	—	0.61
5	7.15	6.10	14.7	0.70	1.10	1.30	0.560	607	20.4	T	S	0.55
6	5.80	5.00	13.8	0.68	1.10	1.50	0.518	745	10.8	T	S	0.44
7	7.10	6.40	9.9	0.47	0.95	1.20	0.585	610	—	L	—	0.55
8	5.70	5.00	12.3	0.56	1.10	1.45	0.534	745	—	I	—	0.53
9	7.00	6.25	10.7	0.46	1.05	1.15	0.560	540	35.2	T	S	0.54
10	6.30	5.00	20.6	0.71	1.20	1.80	0.553	1565	—	T	S	0.49
11	6.45	5.65	12.4	0.56	0.90	1.15	0.599	750	19.8	T	S	0.42
12	6.90	6.25	9.4	0.34	0.95	1.45	0.609	540	7.1	T	N	0.52
13	7.60	6.35	16.5	0.70	0.70	1.00	0.672	550	27.7	T	S	0.58
14	8.05	7.60	5.6	0.23	0.85	1.05	LB	620	10.9	T	S	0.71
15	5.70	4.60	19.3	0.98	1.30	1.50	0.536	530	—	A	S	0.57
16	6.70	5.80	13.4	0.53	1.70	2.60	0.583	966	—	T	S	0.59
17	7.90	7.30	7.6	0.43	1.20	1.60	0.651	490	—	I	—	0.57
18	5.80	4.90	15.5	0.65	1.00	1.30	0.706	633	11.3	T	N	0.50
19	7.30	6.30	13.7	0.58	1.30	1.55	0.570	810	—	I	—	0.54
20	6.90	6.25	9.4	0.82	1.40	1.70	0.800	467	25.3	T	N	0.53
21	7.60	7.10	6.6	0.21	1.00	1.35	LB	720	7.4	T	S	0.56
22	7.60	6.40	15.8	0.72	1.20	1.60	0.693	920	—	T	S	0.48
23	6.00	5.15	14.2	0.80	1.05	1.90	0.646	680	—	L	?	0.50
24	6.80	5.65	17.2	0.68	1.10	1.30	0.684	737	—	I	—	0.53
25	6.90	6.20	10.1	0.60	0.65	1.20	0.746	920	11.9	T	S	0.60
Means and standard deviations (SD)												
Mean (all patients)	6.85	6.03	12.2	0.56	1.11	1.49	0.621	657	19.7			0.53
SD	0.70	0.78	4.1	0.19	0.23	0.36	0.074	172	11.1			0.06
Class I												
Mean	6.18	5.30	14.3	0.64	1.15	1.65	0.588	857	17.2			0.49
SD	0.47	0.41	2.8	0.09	0.24	0.45	0.064	302	7.6			0.05
Classes II and III												
Mean	7.16	6.62	11.3	0.53	1.09	1.42	0.639	645	20.9			0.56
SD	0.58	0.66	4.3	0.22	0.23	0.30	0.076	142	12.6			0.05
Normal												
Mean	4.43	2.86	35.3	1.22	0.91	1.50	0.325	900	9.6			0.44
SD	0.29	0.25	3.7	0.12	0.13	0.29	0.048	151	4.0			0.05

P values

	D_d		D_s		FS		FRS		W_d	
	C	II III	C	II III	C	II III	C	II III	C	II III
M	< 0.001	—	< 0.001	—	< 0.001	—	< 0.001	—	< 0.001	—
I	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	NS	< 0.001	NS	< 0.001	NS

	W_s		PEP/LVET		R R		A/LV		Cardiothoracic Ratio	
	C	II III	C	II,III	C	II III	C	II III	C	II III
M	NS	—	< 0.001	—	< 0.01	—	< 0.001	—	< 0.01	—
I	NS	NS	< 0.01	NS	NS	0.05	< 0.01	NS	< 0.02	< 0.02

Abbreviations A, atrial wave unsatisfactory C control group (normal) I apical impulse impalpable L systolic wave unsatisfactory LB left bundle branch block M, myocardial disease N normal contour S, sustained contour T technically satisfactory I, Class I myocardial disease II III Classes II and III myocardial disease (For other symbols, see text.)

dent noninvasive assessment of myocardial function for both pre ejection and ejection phases of systole

The measurement of systolic time intervals posed no technical problem in our patients with myocardial disease difficulty in recording the aortic component of the second heart sound or in direct carotid pulse is uncommon in these patients. The occasional association of left bundle branch block does however invalidate the PEP/LVET ratio as a test of myocardial function

Apexcardiography The discriminatory value of the A/LV ratio and abnormality of systolic contour was not as great as for FS or PEP/LVET nor are these abnormalities in the apexcardiogram so closely related to changes in the myocardial force velocity relationship On the other hand, most of our patients with technically satisfactory apexcardiograms did demonstrate an increase in the A/LV ratio or an abnormally sustained systolic contour An increased A/LV ratio has been correlated with elevation of the left ventricular end diastolic pressure or exaggeration of the atrial wave in the left ventricular pressure pulse[2,18,19] and, hence reflects left ventricular failure an abnormally sustained apical impulse indicates impairment of base to-apex shortening of the left ventricle due to hypertrophy [20,21] Such information on the presence of left ventricular hypertrophy and failure is, therefore supplementary to detection of abnormal myocardial force velocity relationship from the echocardiogram and measurement of systolic time intervals

The incidence of technical failure was highest for the apexcardiogram. The main reason seems to be variable apposition of the left ventricle and recording transducer depending on the relationship of the apical region of the chamber to intercostal spaces and upon the shape and thickness of the chest wall The incidence of technical failure is therefore unlikely to be further reduced by improvements in instrumentation

Summary

In 25 patients with primary myocardial disease left ventricular myocardial function was assessed by echocardiography systolic time intervals (PEP/LVET ratio) and apexcardiography (A/LV ratio systolic contour) Discrimination of patients with primary myocardial disease from a control group of normal subjects was good for both echocardiography and systolic time intervals best discrimination was obtained by combining data from both of these methods while discrimination by the apexcardiogram or chest roentgenogram was not as clear Fractional shortening the echocardiographic index of myocardial shortening per unit length and the PEP/LVET ratio provide a quantitative assessment of myocardial function which reflects alteration of the myocardial foce velocity relationship by myocardial disease Data from the apexcardiogram are less quantitative but add useful information on the presence of left ventricular hypertrophy or failure Echocardiography is technically the most difficult of the three tests to perform but failure to obtain useful information for technical or other reasons occurs most frequently for apexcardiography All three techniques can be conveniently combined to provide an excellent noninvasive clinical assessment of myocardial function

Thanks are extended to Mrs M Gallant for technical assistance Mrs S Williams for typing and Dr H Feigenbaum for permission to include data on normal subjects studied in his laboratory

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jects with less severe myocardial disease can be detected No such test is currently available Thus although study of a group of patients detected by routine clinical means does facilitate their discrimination from normal subjects this effect is the same for echocardiography, systolic time intervals, and apexcardiography so that a comparison between these tests is still valid and also representative of a patient presenting clinically at the present time

Echocardiography Echocardiography clearly discriminates between normal subjects and asymptomatic (Class I) patients with myocardial disease and provides a quantitative assessment of the severity of impaired myocardial contraction An additional advantage of echocardiography was its ability to define the contribution of left atrial and right ventricular enlargement and of pericardial effusion to cardiac enlargement

Changes in the echocardiographic indices FS and FRS are closely related to changes in the force velocity relationship during ejection Since the left ventricle has been shown to contract in an approximately symmetrical manner about its major axis at least in the absence of localized ischemic damage [10,11] the indices of fractional shortening and fractional rate of shortening are proportional to the extent and rate of left ventricular circumferential shortening Circumferential shortening rate has in fact been estimated from measurements of the left ventricular minor axis both by cineangiography[17] and echocardiography [6] Gault Ross and Braunwald[17] studied five patients with myocardial disease by left ventricular cineangiography the left ventricular minor axis was 7 47cm and shortened by 9 6 per cent during systole, results which are comparable to the values obtained by echocardiography (D_d 6 85 cm and FS 12 2 per cent) Paraskos and co workers[6] derived circumferential shortening rate from echocardiographic measurement and found it to be depressed in patients with impaired left ventricular function at cardiac catheterization [6] It is noteworthy that the simple index FS which reflects extent of left ventricular circumferential shortening discriminated between normal subjects and patients with primary myocardial disease slightly better than did the index FRS which reflects the mean rate of circumferential shortening The reason is that left ventricular failure reduces both the rate and duration of shortening (ejection time) and both of these abnormalities combine to reduce the value of FS

The main disadvantage of ultrasound is the training required to obtain a high quality and reproducible simultaneous recording of echoes from the inner surfaces of the left ventricular wall at the level of the lower margin of the mitral valve leaflets Nevertheless, the incidence of technical failure for the experienced operator is not high and in most instances both the diagnosis and severity of myocardial disease is readily apparent from inspection of the echo pattern during recording of the echocardiogram before indices of myocardial function have been calculated.

Systolic time intervals The index PEP/LVET also clearly distinguished patients with myocardial disease from normal control subjects, thereby confirming earlier observations [13] The normal value obtained in our 25 normal subjects was 0 325 ± 0 048 and is similar to values obtained previously and reported by Weissler, Harris and Schoenfeld[13] for normal volunteer subjects in the basal state (0 345 ± 0 036) and in 24 patients examined during cardiac catheterization (0 334 ± 0 46) In our patients with myocardial disease the PEP/LVET was 0 621 ± 0 074 compared to a value of 0 589 ± 0 094 in six patients with myocardial disease previously reported [3] Systolic time intervals like echocardiography did discriminate clearly between normal subjects and patients with Class I disease, but did not discriminate between patients with myocardial disease in Class I and those in Classes II or III

The excellent correlation found between the PEP/LVET index and the echocardiographic index FS and also the improved discrimination obtained by displaying both indices (Fig 4) is of considerable theoretical interest The relationship of FS to abnormality of the force velocity relationship during left ventricular ejection has already been discussed Similarly, in the absence of left bundle branch block the prolongation of the left ventricular pre ejection period at the expense of the ejection time in patients with myocardial disease has been attributed to a reduced rate of rise of pressure which also reflects alteration of the myocardial force velocity relationship The PEP/LVET ratio and FS therefore provide indepen

Accelerated A-V conduction associated with complete A-V block

Venkatraman Krishnaswami M D *
Anthony R Geraci M D F C C P **
Toledo Ohio

Localization of sites of A V block and the identification of accelerated pathways of conduction have become clinically applicable with the advent of His bundle recordings Identification of the anatomic site of block or the type of pathway in accelerated conduction produces a clearer understanding of the pathogenesis of clinical findings and enables treatment to be more rationally selected in type be this drugs or permanent pacing Routine His bundle electrograms (HBE) are not generally obtained in patients with heart block who require permanent demand pacemakers In our institution however an effort is made to obtain HBE in most patients selected for permanent pacing The information is clinically useful in the follow up of pacemaker patients in an effort to determine the persistance or resolution of varying types of A V block In addition atrial pacing at the time of HBE recording will uncover rate dependent A V blocks display evidence of accelerated conduction if present and estimate sinus node function

In the course of evaluation of a patient with complete heart block associated with a narrow QRS HBE and atrial pacing revealed an intra His bundle block and confirmed an accessory atrial to proximal His bundle pathway

Case report

A 75 year-old white female presented with complaints of dizzy spells, weakness, and fatigue for three *months* These symptoms were insidious in onset and related to effort Syncope or seizures had not occurred In the past she had been treated for hypertension and also experienced recurrent episodes of rapid heart action characterized by abrupt onset and termination She was treated with digitalis for presumed paroxysmal supraventricular tachycardia An electrocardiogram obtained in sinus mechanism revealed a P R of 0 14 sec and a normal QRS There were no delta waves.

Physical examination revealed a regular heart rate of 40 per minute Irregular cannon waves were seen in the neck veins Neurologic examination and a routine chest x ray were normal The electrocardiogram (Fig 1) showed complete heart block with a ventricular rate of 38 per minute and QRS complexes 0 08 second in duration. No evidence of infarction or ischemia was noted The atrial rate was 74 per minute with no capture beats present

Electrophysiologic studies

HBE s were recorded on a multiple channel oscilloscope photographic recorder (Electronics for Medicine White Plains N Y) using a No 7 tripolar electrode (USCI Billerica Mass) introduced from the femoral vein Recordings were made at paper speeds of 150 msec with time lines at 0 1 second intervals Atrial pacing was performed using a bipolar pacing catheter (Medtronic No 5942) positioned against the right atrial wall The resting HBE demonstrated two His bundle potentials (Fig 2) H1 was recorded following the atrial electrogram (A) and H2 preceding the ventricular electrogram (V) with independent A H1 and H2 V activity (Fig 3) The A H1 interval measured 80 msec and the H2 Q interval 37 msec The atria were paced at increasing rates up to 130 per minute and A H1 intervals recorded. Fig 4 demonstrates the absence of an increase in the A H1 interval which remained at 80 msec These findings suggest an A V nodal bypass and an A V block above H2 A permanent bipolar demand pacemaker was then inserted in the usual fashion

From The Department of Medicine and Cardiology The Toledo Hospital and The Medical College of Ohio at Toledo

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Reprint requests to Dr A R. Geraci, Cardiovascular Laboratory The Toledo Hospital, 2142 N Cove Blvd. Toledo, Ohio 43606

* Fellow in Cardiology The Medical College of Ohio at Toledo Toledo Ohio

** Associate Clinical Professor of Medicine The Medical College of Ohio at Toledo, Toledo, Ohio.

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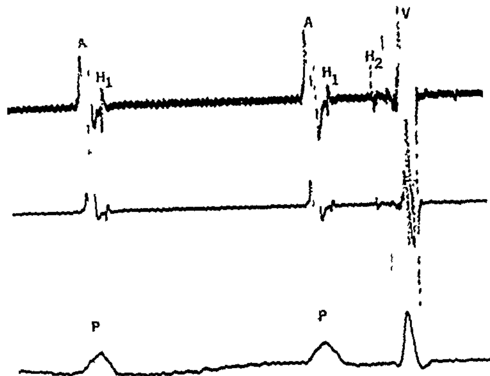


Fig 3 Resting HBE demonstrates H1 potential following the atrial electrogram with an A H1 interval of 80 msec The H2 spike precedes the ventricular potential (V) at H2 Q interval of 37 msec The H1 H2 potentials display independent activity

only via the bypass fiber although both pathways may have functioned intermittently in the past This hypothesis is consistent with the clinical history of intermittent tachycardia previously mentioned. It was because of the history of tachycardia that atrial pacing was performed. The H2 Q interval was constant and unrelated to A H1 activity at rest or during the atrial pacing The narrow QRS is thus consistent with the usual pattern of His bundle rhythms in patients with A H block The finding of intact A H1 conduction and unrelated H2 V conduction suggests that intra His block is present. The failure of A H1 to increase with atrial pacing confirms an alternate atrial to proximal His bundle pathway but does not determine the presence of or block within the A V node as no evidence of conduction through this structure could be demonstrated. Atrial pacing at faster rates or with coupled premature stimulation may have been of value if the refractory period of the accelerated pathway exceeded that of the A V node [4]

The development of complete A V block with the history of supraventricular tachycardia would suggest that if an accelerated pathway is present this can only be of the James fiber type when the QRS complex is narrow and not deformed. A Kent fiber would be expected to conduct the atrial impulses to the ventricle at the sinus rate and conceal the A V block, although deforming the QRS The development of A V block with a Mahiam fiber would result in atrio ventricular dissociation with the initial part of the QRS deformed. A V block in this situation could be A H or H1 H2 The spontaneous development of A V block in this patient successfully terminated the effects of recurring supra ventricular tachycardia by abolishing the conduction of an increased number of impulses to the ventricle The resultant slow ventricular rate following the block was associated with symptoms of decreased cardiac output for which the patient finally sought medical attention

The value of the present information regarding the accelerated pathway and the site of A V block lies in the uncertainty regarding the duration or permanency of this type of block Block distal to the His bundle (H V) is usually permanent and the presence of an accessory A V nodal bypass would not be of great concern A H blocks

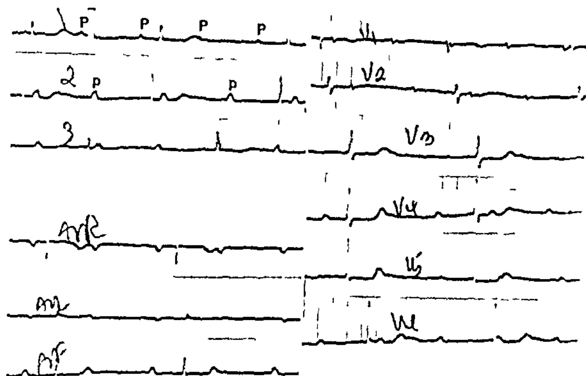


Fig 1 Twelve lead electrocardiogram showing complete heart block with an atrial rate of 74 per minute and a ventricular rate of 38 per minute No capture is noted and the QRS width is normal

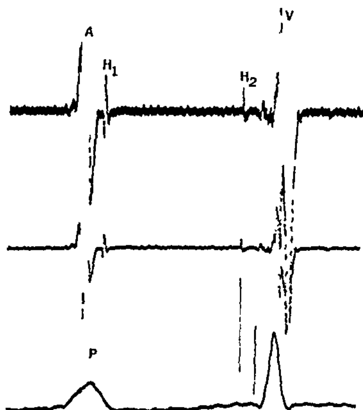


Fig 2 His bundle recording *demonstrating H1 following the* atrial electrogram (A) with an A H1 interval of 80 msec The second His bundle spike (H2) preceding ventricular potential (V) with an H2 Q interval of 37 msec Time lines are at 0 1 second intervals with recording speed of 150 mm per second

Discussion

Many different sites of A V block have been documented with the utilization of His bundle recordings [1,2] Block may occur proximal to the A V node within the A V node (A H) within the His bundle (H1 H2), or distal to the His bundle (H V) The first three types of block are generally associated with a narrow QRS on the surface electrocardiogram in the absence of bundle branch block *The electrocardiogram of the pa* tient reported demonstrated a narrow QRS sug gesting that an A H block would be found The *demonstration of a His bundle spike following* each atrial complex is evidence that a pathway of conduction from the atrial to the proximal His *bundle* is intact A consistent *H2* was found pre ceding the ventricular electrogram and the onset of the QRS on the electrocardiogram These data suggest an intra His block between sites H1 and H2 [3] Conduction through the A V node was not demonstrated as the atrial pacing did not pro *duce an increase in the A H1 interval This find* ing is consistent with complete bypass of the A V node and is defined as a Type III response [4]

Whether an anatomic A V node is present or not cannot be documented It is possible that block of the A V nodal conduction was present at the time of the recording permitting conduction

The Frank scalar atrial vectorcardiogram in normal children

Pedro L Ferrer M D
R Curtis Ellison M D *
Miami, Fla. and Boston, Mass.

Attempts at the differential diagnosis of right atrial and left atrial overload using the standard electrocardiogram have been based primarily on the use of specific times within the P wave or on forces preceding or following notches in various leads With the application of the vectorcardiogram to the study of atrial depolarization by Duchosal and Sulzer[1] and others [2-7] the anterior posterior relationships of the electromotive forces have also been utilized More recently Selvester and co workers[8,9] have utilized timed vectorcardiographic loops in analyzing atrial activity with the Cube system and with the McFee system [10]

This study describes the recording of high gain X, Y and Z tracings of the P wave in normal subjects utilizing the Frank lead system and conventional vectorcardiographic apparatus Numerous measurements of time intervals scalar voltages and spatial voltages were made in an attempt to characterize the differential depolarization of the two atria

Material and methods

Patient material High gain Frank vectorcardiograms were obtained in 115 patients without heart disease at The Children s Hospital Medical Center in Boston Mass between 1969 and 1972 The patients had been admitted for minor surgical procedures orthopedic problems or other illnesses which would not be expected to produce any changes in the cardiovascular system The cardiac evaluation and chest x ray were normal in all patients There were 69 males and 46 females whose ages ranged between two days and 34 years with a median of 6 6 years Twenty seven patients were between birth and six months of age (median age of 1 8 months) 22 patients were between 6 1 months and five years of age (median age of 2 5 years) 42 patients were between 5 1 and 12 years of age (median age of 8 1 years) and 24 patients were between 12 1 and 34 years of age (median age of 15 6 years)

Methods used for recording vectorcardiograms Electrodes were placed in the standard positions for the Frank lead system[11] with the patients in the recumbent position and recordings were made on a Hewlett Packard 1507A vectorcardiographic apparatus. To avoid changes in P wave form produced by marked variations in heart rate or by deep respiratory movements, the tracings analyzed were those obtained during the expiratory phase of respiration with the patients resting quietly High gain recordings of the P wave were made at a sweep speed of 25 mm per second, during which 0 5 mV calibrations were inserted, and at a sweep speed of 100 mm per second for analysis of the P waves Sensitivity was set at 0 5 or 0 2 mV in/volt out (a gain of 2 000× or 5 000× respectively) Eight by 11 inch prints of the expanded X, Y and Z tracings were then obtained using a Documat reader printer In the resulting prints 0 5 mV produced a deflection of 50 or 125 mm whereas each centimeter

From the Department of Cardiology The Children s Hospital Medical Center and the Department of Pediatrics, Harvard Medical School, Boston, Mass.

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Reprint requests Dr Pedro L. Ferrer Pediatric Cardiology 6 5 Mailman Center University of Miami School of Medicine P O Box 875, Biscayne Annex, Miami, Fla 33152.

*Present address Pediatric Cardiology Georgetown University Hospital, 3800 Reservoir Rd., Washington, D C. 20007

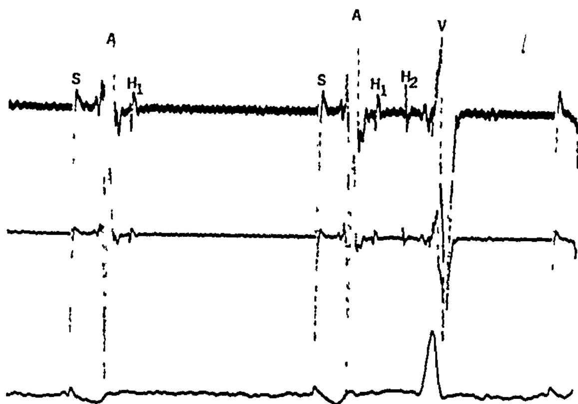


Fig 4 His bundle recording with atrial pacing The A H1 interval remained constant as the atrial pacing rate was increased (80 msec) The H2 V interval and ventricular rate remained unchanged.

however may not be fixed conduction defects and should the patient recover A H conduction the tachycardia may recur Pharmacologic treatment in cases with an accessory pathway is generally unsuccessful and creation of a surgical block could theoretically be required as has been the case in several instances of intractable tachyarrhythmias with accelerated pathways[5] The spontaneous interruption of A H conduction has for the present successfully treated this aspect of the patient s problem The value of recording HBE s in patients with A V block may reveal other examples of intra His block or accelerated pathways which will increase our understanding of these complex problems

Summary

HBE s were recorded in a 70 year old female patient with complete heart block narrow QRS and past episodes of supraventricular tachycardia The HBE revealed split His potentials with intra His block Atrial pacing at increased rates failed to increase the AH1 interval, suggesting an accelerated pathway between the atria and the proximal His bundle bypassing the A V node Below the site of block the ventricles were paced by a distal His bundle (H2) with a resultant normal QRS interval

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ratio between anterior and posterior magnitudes similar to that proposed by Reynolds[13]) and three parameters representing a gross attempt at estimating atrial repolarization. Fig 2 illustrates some of these parameters

Each of the original 40 parameters were analyzed using standard statistical methods Values for the mean median minimal maximal standard deviation, standard error and frequency distribution were obtained for the entire group and for subgroups divided according to age

Results

Table I lists the detailed results of 16 of the original 40 parameters determined in each subject The parameters selected for presentation were those that appeared to be essential for the description of atrial depolarization those which are known from the literature (i e Macruz Index) and those which showed the greatest degree of difference when data from the normal group described here were later compared with data from patients with atrial overload, to be reported in a subsequent paper

The subjects were initially divided into eight groups according to age, but adjacent groups with almost identical values were later combined into four age groups The overall results as well as the changes with age are described in the following sections

General description Our results show that the resultant vector of atrial depolarization moves leftward and inferiorly going anteriorly initially and posteriorly terminally The peak value from the X lead, which measures leftward directed forces occurred at an average time of 51 3 ± 14 2 msec. or at 64 1 per cent of the P duration Only in three of the subjects were small initial forces to the right noted, and in five subjects the initial forces were perpendicular to Lead X

A significant notch occurred in the P wave in Lead X in just over two thirds of the subjects This notch occurred at an average time of 43 8 ± 11 7 msec or at 55 4 per cent of the P duration Almost simultaneously the peak forces in Lead Y representing inferiorly directed forces were noted, occurring at 44 4 ± 10 1 msec or at 55 8 per cent of the P duration. Small superiorly oriented forces in the terminal portion of atrial depolarization were noted in seven cases A significant notch was noted in Lead Y in two thirds of the subjects occurring at an average time of 39 3 ± 13 6 msec or 48 5 per cent of the P duration

At the same time that the forces are moving leftward and inferiorly they are initially moving anteriorly This anterior direction is recorded as a negative deflection on Lead Z. The maximum forces anteriorly directed occurred at 29 6 ± 7 6 msec or at 37 3 per cent of the P duration (AT_c for anterior time corrected) The electromotive forces then went posteriorly crossing the base line at an average time of 47 9 ± 13 msec or at 59 7 per cent of the P duration (APT_c for anterior posterior time, corrected) and reached a maximum value posteriorly at 60 3 ± 15 msec or at 75 per cent of the P duration (PT_c for posterior time corrected) In only eight patients were there no posterior forces recorded The maximum voltage to the left while Z is positive or left posterior forces (LPF) occurred at an average time of 56 0 ± 13 0 msec or 70 per cent of the P duration

P duration and PR interval The duration of atrial activation or P duration (P Dur) showed a significant increase with age as shown in Table I The duration of the PR interval (PR Int) and the PR segment also increased progressively with age There was a slight tendency for a greater increase in the duration of the P wave than in the duration of the PR segment Thus the ratio

$$\frac{\text{P Dur}}{\text{PR Int} - \text{P Dur}}$$

or the Macruz Index showed a tendency for increased values with age although the changes were not statistically significant

Scalar magnitudes and times. The maximum leftward forces (X+) showed the highest values in the youngest group and the lowest values in the group over 12 years of age (Table I) The maximum inferior forces (Y+) did not show a clear tendency

The most interesting changes with age were noted in the values for the maximum anterior forces (Z−) and maximum posterior forces (Z+) The anterior forces tended to remain relatively stable with age while the posterior forces (Z+) decreased progressively with age Because of the progressive decrease of Z+ the ratio between anterior and posterior forces

$$\left[\frac{Z-}{(Z-)+(Z+)} \right]$$

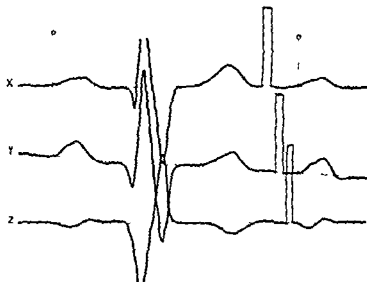


Fig 1 Determination of the isoelectric lines for the atrial vectorcardiogram A line joining the onset (0) of atrial depolarization of two consecutive beats forms the isoelectric line for each lead

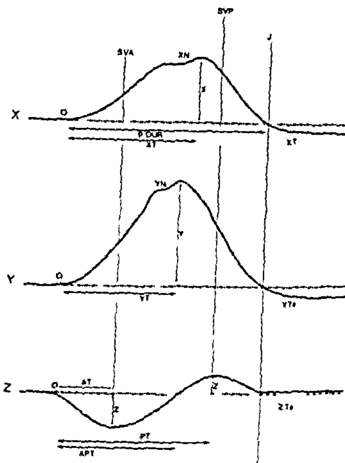


Fig 2 Normalized drawings of X, Y and Z recordings of the P wave using the Frank lead system O = onset of P wave J_a = end of atrial depolarization P Dur = duration of P wave X+ = maximum leftward forces Y+ = maximum inferior forces Z− = maximum anterior forces Z+ = maximum posterior forces SVA = spatial voltage at time of maximum anterior forces SVP = spatial voltage at time of maximum posterior forces XN = notch in lead X, YN = notch in lead Y XT = time of maximum leftward forces YT = time of maximum inferior forces AT = time of maximum anterior forces APT = time of shift between anterior and posterior forces PT = time of maximum posterior forces XT_a = portion of T_a wave in PR segment in Lead X, YT_a = portion of T_a = wave in PR segment in Lead Y ZT_a = portion of T_a wave in PR segment of Lead Z

of the horizontal axis corresponded to approximately 20 msec

Methods for measuring atrial vectorcardiograms The beginning of the P wave was identified as the first point of deflection of any of the three leads and all timings originated at this point The base line for each of the three leads was established as a horizontal line which passed through the supposedly isoelectric point where the end of the previous T or U wave joined with the beginning of the P wave and connected to the similar point of the following cycle (Fig 1) Slow sweep tracings were used to help in the determination of the base line The end of atrial depolarization (J_a point) was established at the last point of intersection between any of the three leads (except for a lead where persistent elevation of the PR segment was present) and the base line previously determined The P duration was measured from the onset of P to J_a PR segment between the J_a point and the onset of QRS, and PR interval from the onset of the P wave to the onset of QRS

Voltages were determined for the three leads at 2 5 msec intervals Spatial voltages at each 2 5 msec interval were also calculated by squaring the magnitude of each of the simultaneous X Y and Z leads and then taking the square root of the sum The directions of each vector as projected on to the frontal plane (the elevation) and as projected on to the horizontal plane (the azimuth) were calculated A 360 degree circle was used for both determinations with the patients left side being 0 degrees Measurements from the 8 by 11 inch prints of the expanded X Y and Z leads were made utilizing an X Y digitizing table connected on line to a Digital Equipment Corporation PDP 9 computer

Parameters determined Forty different parameters were studied in each patient These included P duration and PR interval time intervals when selected electromotive forces or notches occurred magnitude of scalar voltages from the X, Y and Z leads spatial voltages at selected times and their direction ratios between selected times and voltages (including the Macruz Index[12] and a

Table I Cont'd

Median Age / No. of patients		Group I NB-6 mo: 1.8 mo, 27	Group II 6 mo–5 yr: 2.5 yr, 22	Group III 5 yr–12 yr: 8.1 yr, 42	Group IV > 12 yr: 15.6 yr, 24	Entire group: 6.6 yr, 115
Scalar magnitudes—cont'd						
Y+ (μV)	5th	45	25	43	55	48
	10th	62	64	55	69	68
	50th	112	135	114	150	124
	90th	175	175	187	171	179
	95th	189	191	202	189	193
	Mean ± S.D.	114 ± 43	134 ± 41	118 ± 47	137 ± 45	124 ± 45
Z− (μV)	5th	6	18	20	18	18
	10th	11	22	24	20	20
	50th	40	44	43	36	41
	90th	72	65	62	67	65
	95th	92	76	80	76	77
	Mean ± S.D.	41 ± 24	45 ± 15	44 ± 16	40 ± 17	43 ± 18
Z+ (μV)	5th	0	1	1	1	0
	10th	18	14	18	9	15
	50th	42	30	27	20	29
	90th	76	64	54	57	58
	95th	85	67	57	61	65
	Mean ± S.D.	40 ± 24	32 ± 19	30 ± 16	26 ± 18	32 ± 18
LPF (μV)	5th	0	5	7	6	0
	10th	0	34	48	30	37
	50th	73	75	66	57	69
	90th	147	127	86	86	106
	95th	168	139	105	96	122
	Mean ± S.D.	78 ± 46	72 ± 32	67 ± 21	57 ± 21	69 ± 31
Spatial magnitudes and directions						
MSVL (μV)	5th	80	18	74	69	72
	10th	89	57	81	78	83
	50th	138	128	114	119	124
	90th	199	187	146	176	183
	95th	208	208	163	184	189
	Mean ± S.D.	144 ± 40	128 ± 47	114 ± 25	126 ± 37	126 ± 38
$MSVL_{Az}$ (degrees)	5th	318	317	328	324	323
	10th	324	320	329	334	328
	50th	356	348	351	2	355
	90th	22	32	18	31	24
	95th	26	36	31	36	31
	Mean ± S.D.	352 ± 21	351 ± 22	353 ± 18	2 ± 21	355 ± 20
SVA (μV)	5th	52	50	41	42	50
	10th	65	57	53	65	60
	50th	113	91	93	104	99
	90th	182	145	134	168	151
	95th	201	150	150	173	167
	Mean ± S.D.	117 ± 42	94 ± 31	93 ± 30	109 ± 37	102 ± 36

Table I *Normal values for selected parameters from the Frank scalar atrial vectorcardiogram (Presented as fifth, tenth, fiftieth, ninetieth, and ninety fifth percentiles and as mean ± 1 standard deviation)*

		Group I *NB 6 mo*	*Group II* *6 mo 5 yr*	*Group III* *5 yr 12 yr*	*Group IV* *> 12 yr*	*Entire group*
Median Age *No of patients*		*1 8 mo* *27*	*2 5 yr* *22*	*8 1 yr* *42*	*15 6 yr* *24*	*6 6 yr* *115*
General						
P Dur (msec)	5th	44	58	67	75	55
	10th	48	64	77	77	60
	50th	65	78	84	91	82
	90th	85	90	95	103	95
	95th	89	92	102	114	100
	Mean ± S D	63 ± 12	77 ± 9	85 ± 8	91 ± 10	80 ± 14
PR Int (msec)	5th	84	97	103	108	91
	10th	87	108	112	126	101
	50th	108	125	133	140	130
	90th	124	146	161	165	160
	95th	126	146	161	165	160
	Mean ± S D	107 ± 13	125 ± 15	137 ± 20	144 ± 17	120 ± 21
$\frac{\text{P Dur}}{\text{PR Int P Dur}}$ (Macruz index)	5th	0 82	1 10	0 89	0 92	0 91
	10th	0 91	1 13	1 08	1 19	1 13
	50th	1 41	1 56	1 75	1 85	1 61
	90th	2 72	3 46	2 76	2 68	2 67
	95th	3 23	3 99	2 89	4 18	3 05
	Mean ± S D	1 58 ± 0 61	1 80 ± 0 80	1 81 ± 0 58	1 93 ± 0 77	1 78 ± 0 68
Times						
AT_c (% of P Dur)	5th	19	20	27	26	24
	10th	23	25	28	27	27
	50th	40	35	37	37	37
	90th	62	43	51	48	48
	95th	64	45	56	51	53
	Mean ± S D	39 ± 11	34 ± 17	38 ± 9	37 ± 7	37 ± 9
APT_c (% of P Dur)	5th	32	40	44	44	43
	10th	42	42	47	48	47
	50th	54	57	60	59	58
	90th	76	83	74	85	78
	95th	96	87	80	91	84
	Mean ± S D	59 ± 14	57 ± 13	61 ± 10	62 ± 14	60 ± 12
Scalar magnitudes						
X+ (μV)	5th	44	38	47	42	45
	10th	61	43	54	46	41
	50th	100	76	76	66	76
	90th	167	127	95	93	117
	95th	188	139	117	97	134
	Mean ± S D	102 ± 37	78 ± 26	76 ± 17	69 ± 17	81 ± 27

Abbreviations P Dur = P duration PR Int = PR interval AT_c = anterior time corrected (time of maximum anterior forces divided by P duration) APT_c = anterior posterior time corrected (time of the shift between the anterior and posterior forces divided by P duration) X+ = maximum leftward forces Y+ = maximum inferior forces Z = maximum anterior forces Z+ = maximum posterior forces LPF = maximum left posterior forces (maximum voltage to the left while Z is positive) *MSVL* = *maximum spatial voltage to the left* $MSVL_A$ = *azimuth of maximum spatial voltage to the left* SVA = spatial voltage anterior SVP = spatial voltage posterior $\frac{Z-}{(Z-)+(Z+)}$ = ratio between maximum anterior and maximum posterior forces $\frac{SVA}{SVA+SVP}$ = ratio between spatial voltages at the time of maximum anterior and maximum posterior forces

Discussion

The anatomic position of the SA node to the right superior and posterior the position of both atria particularly in their anterior posterior relationship[14] and the sequence of normal excitation of the atrium[15,16] explain why the P vector as a resultant of the electromotive forces produced during atrial depolarization, goes to the left inferiorly and initially anteriorly and later posteriorly There is an important difference between atrial and ventricular depolarization In the former both right and left atria are depolarized largely from right to left whereas in the latter the excitation process spreads from the ventricular septum both rightward and leftward Therefore during ventricular excitation rightward forces tend to represent right ventricular forces and leftward forces tend to represent left ventricular forces During atrial depolarization however, an increase in the leftward forces could represent an increase in either right or left atrial forces

The traditional approach to separating right and left atrial depolarization has been based on the work of Puech and co workers[15] and other early investigators demonstrating that right atrial depolarization largely precedes left atrial depolarization although there is a period of overlap of the activation of the two atria Separation of the P wave into right atrial and left atrial portions has relied largely on notches occurring in the various leads This approach has been challanged by Brody and co workers[17] and our own results also suggest that notches are unreliable landmarks for separating right from left atrial forces. A significant notch in Lead X was seen in only 69 6 per cent of our subjects and a notch in Y in 67 per cent. Frequently more than one notch was present Also there was a marked variability in the time of occurrence of the notches in these normal subjects

Spach and co-workers[16] have published the sequence in which the atrial structures are being activated and the average times at which these events occur in dogs. In order to utilize these times as a model of atrial excitation, we calculated them as percentages of the P duration using a value of 65 msec for normal P duration in the dog

Using these values the timing of atrial activation in the dog can be summarized as follows During the initial 36 to 40 per cent of the P duration there is considerable activity over the right atrium with no change over the left atrium At approximately 49 to 53 per cent of the P duration the last parts of the right atrium are being depolarized and two major wave fronts are formed over the left atrium At approximately 69 to 86 per cent of the P duration the major areas of the left atrium are being activated. Although results in dogs may not be entirely comparable to human atrial excitation, studies by Durrer and co workers[18] in two normal isolated human hearts also suggest that the beginning of the major wave fronts in the left atrium occurs around 45 to 50 per cent of the P duration

In our results the maximum leftward forces (X+) were found to occur at an average time of about 64 per cent of the P duration which according to the model described by Spach would be when the left atrium is being activated The maximum inferior forces (Y+) occurred at an average time of 56 per cent of the P duration thus coming at a time when right atrial depolarization is being completed and the major wave fronts are just beginning over the left atrium The fact that the maximum inferior forces occur prior to the major left atrial depolarization would suggest that the wave fronts over the right atrium are more inferiorly directed than those over the left atrium which are more laterally directed.

The maximum anterior forces (Z−) occurred at 37 per cent of the P duration which corresponds quite well with the major right atrial depolarization in the experimental model. The maximum posterior forces (Z+) occurred at 75 per cent of the P duration corresponding in the experimental model to the time when the major portions of the left atrium are being activated. The electrophysiologic studies[16] further suggest that leftward and posterior forces might also reflect left atrial depolarization In our studies the maximum leftward posterior forces (LPF) occurred at an average time of 70 per cent of the P duration again corresponding to major depolarization times over the left atrium. There were eight of our subjects (7 per cent) who did not demonstrate any posterior forces in their atrial vectorcardiograms In five of these cases certain features of the vectorcardiogram seemed to clearly separate right from left atrial depolarization The right atrial forces appeared to be represented by

Table I Cont d

		Group I NB 6 mo	Group II 6 mo 5 yr	Group III 5 yr 12 yr	Group IV > 12 yr	Entire group
Median Age No of patients		1 8 mo 27	2 5 yr 22	8 1 yr 42	15 6 yr 24	6 6 yr 115
Spatial magnitudes and directions—cont d						
SVP (μV)	5th	0	3	2	7	0
	10th	0	23	35	39	30
	50th	110	115	82	68	92
	90th	189	195	126	160	166
	95th	196	213	157	179	185
	Mean ± S D	109 ± 58	113 ± 58	85 ± 38	84 ± 44	96 ± 50
Ratios						
$\frac{Z-}{(Z-)+(Z+)}$	5th	0 09	0 23	0 30	0 33	0 23
	10th	0 15	0 38	0 31	0 38	0 31
	50th	0 51	0 59	0 61	0 64	0 58
	90th	1 00	0 86	0 81	0 94	0 88
	95th	1 00	0 98	0 99	0 99	1 00
	Mean ± S D	0 45 ± 0 22	0 59 ± 0 16	0 58 ± 0 16	0 61 ± 0 19	0 56 ± 0 18
$\frac{SVA}{SVA + SVP}$	5th	0 28	0 28	0 31	0 34	0 32
	10th	0 33	0 31	0 35	0 35	0 34
	50th	0 51	0 44	0 53	0 56	0 51
	90th	1 00	0 80	0 78	0 80	0 80
	95th	1 00	0 84	0 88	0 82	0 90
	Mean ± S D	0 49 ± 0 13	0 46 ± 0 14	0 54 ± 0 17	0 56 ± 0 13	0 51 ± 0 14

showed higher values with increasing age as seen in Table I The maximum value of X when Z is positive (LPF) also showed larger values for infants than for older children

The times of occurrence of X+ Y+, Z− and LPF when corrected for P duration were essentially unchanged by age The time at which Z becomes positive (APT_c) had a tendency to increase with age, but the changes were not significant The time at which Z+ occurred increased significantly in the older age groups when compared with the two younger groups Thus, with increasing age, posterior forces tended to decrease and the time of their occurrence became progressively delayed

Spatial magnitudes and directions Maximum spatial voltage to the left (MSVL) showed a tendency to decrease with age (Table I) For the entire group MSVL averaged 126 4 μV and was directed slightly posteriorly (mean azimuth = 355 degrees) and inferiorly (mean elevation = 45 degrees)

Spatial voltages were also measured at the time of the maximum anterior forces termed spatial voltage anterior (SVA), and at the time of the maximum posterior forces termed spatial voltage posterior (SVP) SVA averaged 102 μV with a mean azimuth of 49 degrees and a mean elevation of 60 degrees

The mean value for SVP for the entire group was 96μV Although there was a tendency for lower values in the older groups of patients the differences were not significant The mean azimuth of SVP was 328 degrees and the mean elevation was 41 degrees

The relationship between the spatial voltage anterior and the spatial voltage posterior was expressed as

$$\frac{SVA}{SVA + SVP}$$

The mean value of this ratio for the entire group was 0 51 The highest values for this ratio were found in the two older groups of patients

Right atrial activity was reflected in leftward, inferior and anterior forces while left atrial depolarization began later and was reflected in leftward, inferior and more posterior forces Normal values of selected parameters are presented.

The study indicates that high gain recordings of the scalar atrial vectorcardiogram can be easily obtained as a part of a routine vectorcardiographic procedure Readily determined parameters reflect differential depolarization of the right atrium and of the left atrium

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Z– or SVA and left atrial forces by X+ or MSVL In the other three patients, good separation of anterior right atrial forces from more leftward left atrial forces was not evident

Another time relationship of interest which would correspond to the "horizontal crossing time X" described by Duchosal, Odier, and Boufas,[19] is the time when the P vector becomes posterior in the horizontal plane (APT_c) This occurred at 60 per cent of the P duration in our subjects Using the experimental model again for comparison, it can be seen that right atrial depolarization has been completed and left atrial depolarization begun prior to the time that the forces become posterior, although the major left atrial depolarization occurs after this time

As was true with the quantitative analysis of ventricular depolarization found in earlier studies [20] spatial voltages appeared to be useful in the quantitation of atrial depolarization as well Since both right and left atria are depolarized largely in a rightward to leftward direction, it would be anticipated that the maximum spatial voltage to the left (MSVL) would be increased in both right and left atrial overload This was found to be the case in a small series of patients studied by Duchosal, Odier, and Boufas[19] and in our own experience in patients with heart disease to be presented in a subsequent publication

As we have mentioned the times that the maximum anterior and posterior forces occur correlate well with times of maximum right atrial depolarization and left atrial depolarization, respectively in the experimental model Therefore it seems logical that the spatial voltage measured at the time of the maximum anterior forces (SVA) and the spatial voltage measured at the time of the maximum posterior forces (SVP) would also represent right and left atrial depolarization Our studies in patients with right or left atrial overload support this contention

The Macruz Index[12] was found to be somewhat higher in our study than the values recorded from normal subjects in the literature [22,23] This might be expected from the fact that we measured the P duration from the simultaneous X, Y, and Z leads, selecting as the end of the P wave the point where the last of these three leads crossed the isoelectric line Thus our values for P duration and also Macruz Index would be somewhat higher than if the measurements of P duration were made from only a single lead. Because of the wide variability of the values of the Macruz Index for normal subjects one would suspect that it may not be a sensitive means of diagnosing atrial overload

In addition to the changes in P duration and PR interval that occurred with increasing age, the most striking change was a tendency for a decrease in the leftward and posterior forces Also, the time of occurrence of the maximum posterior forces (PT_c) was delayed in the older patients It is not known whether these changes represent anatomic or physiologic changes which occur within the atria themselves, or whether changes in the torso of the growing child somehow produce these variations In any case, an age dependent scale is necessary for assessing these parameters.

The Frank lead system is currently being used widely in this country to obtain loops and scalar recordings of the QRS complex. This study has demonstrated that it is possible to record high gain tracings of atrial activity utilizing just the standard type of vectorcardiographic apparatus. The parameters are all obtainable from the X, Y, and Z leads which are more conveniently analyzed than loops, whether by hand or by computer The three leads are recorded simultaneously, making the determination of spatial voltages accurate and practical The scalar tracings also make it possible to assess time intervals and heart rate and rhythm quite easily

This study further indicates that parameters from the atrial vectorcardiogram in children relate well to patterns of atrial depolarization demonstrated in the experimental laboratory The results from normal subjects presented here should form a basis for detecting atrial overload in patients with heart disease

Summary

High gain recordings of the Frank scalar atrial vectorcardiogram were obtained with conventional vectorcardiographic apparatus in 115 normal subjects Forty measurements of time intervals scalar voltages, and spatial voltages which were expected to most likely reflect patterns of depolarization found in the experimental laboratory, were selected for analysis

The atrial vectorcardiogram was found to relate well to patterns of right and left atrial depolarization previously described in dogs

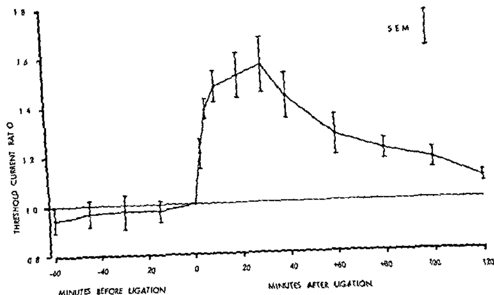


Fig 1 Changes in threshold defibrillation current before and following myocardial infarction

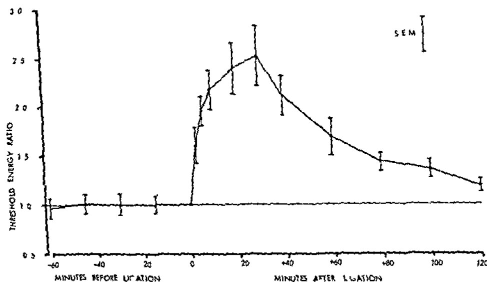


Fig 2 Changes in threshold defibrillation energy before and following myocardial infarction

size If defibrillation was achieved, the heart was refibrillated after a 30 second recovery period to allow perfusion of the heart prior to the next trial. In the next trial defibrillation was attempted using approximately 10 per cent less voltage than in the previous trial. This procedure was repeated using successive 10 per cent decrements in voltage until a defibrillation attempt failed, whereupon the voltage was increased to a level adequate to defibrillate. If the original attempt to defibrillate was unsuccessful the voltage was raised by 10 per cent increments until defibrillation was accomplished The threshold voltage and current were taken as the lowest values which defibrillated the ventricles In order to prevent deterioration of ventricular function fibrillation was never allowed to persist for longer than 30 seconds If a series of 10 per cent

Electrical threshold for defibrillation of canine ventricles following myocardial infarction

W A Tacker, Jr, M D, Ph D
L A Geddes M E, Ph D
P S Cabler B S
A G Moore
Houston Texas

Within the past two decades the technique of electrical ventricular defibrillation has become an established lifesaving procedure It is used by the cardiovascular surgeon to restore normal pumping activity to the ventricles which are often purposely fibrillated during surgery The technique is also used to terminate ventricular fibrillation in nonsurgical patients the majority of which are patients with myocardial ischemia usually myocardial infarction The strength of countershock energy is determined empirically, and no dosage schedule is available to guide the physician in his choice of shock strength Recently our group reported an electrical dosage schedule for both trans chest and direct countershock for reversion of ventricular fibrillation in large and small animals [1,2] The animal data have since been verified in humans [3] The ability to accurately quantitate the shock strength requirements for normal hearts has made possible the investigation of the observation that acute myocardial ischemia makes the ventricles considerably more difficult to defibrillate The following studies were, therefore, carried out to quantitate the changes in the strength of the electrical countershock required for defibrillation of the ventricles following myocardial infarction

Methods and materials

Fourteen dogs were employed in this study they were divided into two groups and designated Group A and Group B After anesthetization with intravenous pentobarbitol (30 mg per kilogram) the trachea was intubated and artificial respiration was applied The thorax was opened via a median sternotomy and the heart was exposed by excision of the ventral pericardium Femoral artery blood pressure and a Lead II electrocardiogram (ECG) were monitored continuously Fibrillation was induced by applying a one second burst of 60 Hz 2 msec duration square wave stimuli of 20 volts peak intensity to the ventricles using a hand held bipolar stimulating electrode It was not always necessary to induce ventricular fibrillation because it frequently occurred spontaneously following infarction of the myocardium Ventricular fibrillation was confirmed by direct visualization of the disorganized fibrillatory contractions of the heart fibers loss of femoral artery blood pressure and appearance of fibrillation waves in the ECG

The defibrillator employed in this study has been described previously [4] It delivers a single half sinusoidal current pulse having a duration of 8 33 msec The output of the defibrillator could be varied continuously from 0 to 1 000 volts peak The peak voltage and current values for each defibrillation trial were measured using a two channel storage oscilloscope (Model 564 Tektronix, Portland Ore) Threshold current and energy values were determined in the following manner the ventricles were fibrillated and a pair of concave oval (6 by 9 cm) metal defibrillating electrodes were applied firmly to the lateral sides of the heart The heart weight (in grams) was estimated and defibrillation was attempted using a voltage estimated to be adequate for that heart

From the Department of Physiology Baylor College of Medicine Texas Medical Center Houston Texas

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Reprint requests Dr W A Tacker Dept of Physiology Baylor College of Medicine Houston Texas 77025

Table IB Ventricular defibrillation Energy threshold ratios for individual subjects

Dog No	*Control preinfarction time*					*Experimental postinfarction time*									
	-60	*-45*	*-30*	*-15*	*0*	*3*	*6*	*10*	*20*	*30*	*40*	*60*	*80*	*100*	*120*
1	0 99	1 02	1 16	1 04	1 00	1 14	1 57	2 16	2 14	2 23	2 14	1 16	1 01	1 20	1 24
2	0 75	0 73	0 49	0 79	1 00	1 19	1 38	1 25	0 95	0 99	1 05	1 35	1 31	1 16	0 99
3	1 27	1 14	1 01	1 00	1 00	2 21	3 42	2 63	2 34	2 28	2 13	2 23	1 63	1 70	0 98
4	0 69	0 80	0 89	0 95	1 00	1 25	1 50	2 00	2 14	1 55	1 07	0 78	1 31	1 04	0 90
5	0 84	0 90	0 85	0 74	1 00	0 87	2 45	4 03	4 53	3 87	2 98	2 45	1 73	1 33	1 05
6	1 21	1 48	1 52	1 47	1 00	1 34	1 68	1 83	1 96	2 03	1 89	0 95	1 23	1 60	1 41
7	–	–	1 11	1 04	1 00	1 17	1 34	1 37	1 28	1 62	1 82	1 54	1 57	1 14	0 91
8	–	–	–	–	1 00	1 21	1 38	1 52	1 85	2 80	2.82	2.15	–	–	–
9	–	–	–	–	1 00	3 16	2 21	2 13	1 91	1 85	1 79	1 25	1 41	1 58	1 61
10	–	–	–	–	1 00	1 41	2 00	2 93	2 78	2 64	2 49	2 32	1 89	2 13	1 43
11	–	–	–	–	1 00	1 39	1 86	2 69	3 88	5 35	2 54	1 15	1 15	0 96	1 08
12	–	–	–	–	1 00	1 85	2 55	2 89	2 72	2 81	2.91	2 37	1 26	1 31	1 31
13	–	–	–	–	1 00	1 36	2 00	1 36	2 91	3 45	3 09	2 91	2 11	1 36	1 33
14	–	–	–	–	1 00	2 86	1 99	1 40	1 66	1 58	0 79	0 77	0 91	1 09	1 13
AVE.	0 96	1 01	1 00	1 00	1 00	1 60	1 95	2 16	2 38	2 50	2 10	1 67	1 43	1 35	1 18
SEM	0 10	0 11	0 12	0 09	0 00	0 18	0 15	0 21	0 26	0 30	0 20	0 19	0 09	0 09	0 06
SD	0 24	0 27	0 32	0 24	0 00	0 68	0 57	0 80	0 96	1 15	0 75	0 71	0 34	0 32	0 22

P ak val e for this subject

bles IA and IB The data have been normalized in the following manner In each subject the pre occlusion current and energy values were used as reference levels The postocclusion values were expressed as ratios of this reference value For example in dog No 1 (see Tables 1A and B) the defibrillation threshold measured after 60 min utes of control time and three minutes prior to occlusion was 4 84 amperes of current and 1 19 watt seconds of energy Thus the threshold cur rent at 15 minutes pre infarction which was 5 06 amperes, is expressed in the Table as a ratio of $\left(\frac{5\ 06}{4\ 84}\right)$ = 1 05 Likewise the pre infarction en ergy value of 1 19 watt seconds is expressed as equal to unity and the 15 minute preinfarction value of 1 24 watt seconds is expressed as the ratio $\left(\frac{1\ 24}{1\ 19}\right)$ = 1 04 and so on. This method of expressing threshold differences as ratios has been previously reported by the authors [4]

Inspection of Tables IA and B as well as Figs 1 and 2 reveal that following infarction there was a marked increase in both current and energy thresholds. The average peak increase occurred at 30 minutes after infarction and the maximum average increase in current was to a ratio of 1 55 (55 per cent above the pre occlusion value) max imum average energy increased to a ratio of 2 5 (150 per cent above the pre occlusion value) After 30 minutes the average threshold re turned toward but did not reach control values At 120 minutes the average ratio for current was 1 08 (8 per cent above control) whereas the average ratio for energy was 1 18 (18 per cent above the pre occlusion value) Inspection of the Tables reveals considerable variation in the peak increase and time course of threshold changes in the individual subjects The earliest peak occur red in animals No 9 and No 14 (at three min utes) and the latest in animals Nos 7, 8 and 12 (at 40 minutes) The greatest increase in energy and current threshold was in animal No 11 (cur rent increased 136 per cent energy increased 435 per cent) The least increase was in animal No 2 (current increased 13 per cent energy in creased 38 per cent)

Discussion

It is readily apparent that myocardial ischemia consistently produces a rapid increase in the threshold current and energy required for ven tricular defibrillation of canine ventricles This increased requirement peaks rapidly and then returns toward control (pre infarction) values At two hours after infarction the elevation above control level is insignificant It is not surprising to find supportive human data for this phenome non in the medical literature Lindsmith[5] re ported that during implantation of an aortic

Table IA Ventricular defibrillation Current threshold ratios for individual subjects

Dog No	*Control preinfarction time*					*Experimental postinfarction time*									
	−60	*−45*	*−30*	*−15*	*0*	*3*	*6*	*10*	*20*	*30*	*40*	*60*	*80*	*100*	*120*
1	0 91	0 96	1 05	1 05	1 00	1 06	1 24	1 45	1 56	1 49	1 46	1 09	0 99	1 12	1 09
2	0 81	0 81	0 62	0 64	1 00	1 07	1 13	1 03	0 81	0 78	0 81	0 97	1 17*	1 11	0 99
3	1 15	1 08	1 01	1 00	1 00	1 34	1 67*	1 54	1 48	1 46	1 44	1 57	1 31	1 35	1 00
4	0 84	0 88	0 93	0 96	1 00	1 12	1 23	1 43	1 46*	1 20	0 93	0 88	1 22	1 08	1 01
5	0 94	0 95	0 96	0 92	1 00	0 84	1 43	2 00	2 16*	2 03	1 85	1 64	1 36	1 04	1 04
6	1 01	1 14	1 19	1 17	1 00	1 13	1 26	1 30	1 30*	1 30	1 24	0 87	1 06	1 15	1 11
7	–	–	1 00	0 85	1 00	1 10	1 21	1 22	1 14	1 26	1 38	1 24	1 19	1 06	1 01
8	–	–	–	–	1 00	1 23	1 39	1 44	1 57	1 90*	1 90	1 62	–	–	–
9	–	–	–	–	1 00	1 76	1 53	1 48	1 35	1 35	1 35	1 18	1 22	1 29	1 24
10	–	–	–	–	1 00	1 17	1 38	1 65*	1 64	1 61	1 69	1 47	1 41	1 47	1 24
11	–	–	–	–	1 00	1 17	1 37	1 71	1 96	2 36*	1 57	1 05	1 05	1 00	1 05
12	–	–	–	–	1 00	1 32	1 45	1 55	1 64	1 66	1 62	1 41	1 11	1 09	1 05
13	–	–	–	–	1 00	1 00	1 59	1 53	1 71	2 00	1 81	1 71	1 51	1 16	1 06
14	–	–	–	–	1 00	1 53*	1 38	1 28	1 38	1 34	0 98	1 00	1 05	1 14	1 13
AVE	0 94	0 97	0 97	0 97	1 00	1 20	1 38	1 47	1 51	1 65	1 42	1 26	1 20	1 16	1 08
SEM	0 05	0 05	0 07	0 04	0 00	0 06	0 04	0 06	0 09	0 11	0 09	0 08	0 04	0 04	0 02
SD	0 12	0 12	0 17	0 12	0 00	0 23	0 15	0 23	0 33	0 41	0 34	0 30	0 16	0 13	0 08

Peak value for this subject.

voltage increases failed to defibrillate within that time defibrillation was accomplished with an adequately high voltage and the trials were resumed after a 30 second perfusion period

Using the procedures just described defibrillation thresholds were measured before and after myocardial ischemia had been produced by occlusion of the left intraventricular coronary artery Group A included the seven control animals and in these subjects control values for defibrillation thresholds during a 60 minute period were determined before infarction but following the preliminary surgical procedure Cardiac surgery consisted of sharp and blunt dissection of the left interventricular coronary artery such that a 0 5 cm length was freed from surrounding fatty tissue and coronary veins A silk ligature was then passed loosely around the free portion of the artery but was not tied at this time The level of dissection and suture placement was approximately 2 0 cm distal to the origin of the left coronary artery Multiple baseline (control) defibrillation thresholds were successively determined over a period of one hour immediately following this surgical procedure

The ligature was then securely tied around the coronary artery and adequacy of occlusion confirmed by (1) appearance within 30 seconds of darkening of the area of myocardium supplied by the occluded vessel, (2) dilation of the discolored area associated with systolic bulging of the ventricular wall involved, and (3) appearance of S T segment changes in the ECG indicative of anterolateral myocardial wall infarction After ligation, defibrillation threshold values were measured by fibrillating the ventricles at selected times during the two hours following coronary artery occlusion In some instances the ventricles fibrillated spontaneously and when this occurred, defibrillation was carried out immediately

The protocol for the seven dogs in Group B was identical to that of Group A except that the 60 minute control period was excluded In one animal in Group B the experiment was terminated at 60 minutes after occlusion because of technical difficulty with the recording equipment

Threshold current, voltage and duration for each trial were measured directly from the oscilloscope The energy for each trial was calculated from the expression

$$Energy = E_m \times I_m \times \frac{d}{2}$$

where E_m = peak voltage I_m = peak current and d = duration of the half sinusoidal pulse

Results

The changes in threshold current and energy for each of the fourteen subjects are shown in Ta

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valve prosthesis acute myocardial infarction occurred in a patient and following the infarction involving the anterolateral wall of the left ventricle electrical ventricular defibrillation could not be accomplished For this reason the infarcted area was excised, after which fibrillation was easily converted to a sinus rhythm by electrical countershock Subsequently DeBakey, Diethrich, and Liddicoat[6] encountered similar difficulty in a patient who had an acute myocardial infarction of the left ventricle during double valve prosthesis implantation Following infarctectomy, defibrillation was successful In these two cases, removal of the infarcted area apparently lowered the electrical defibrillation threshold It would appear from the data reported herein that this could have been due to either of two things (1) removal of the ischemic tissue and/or (2) passage of time Certainly, the experimental animal data indicate that the increase in threshold is of only minutes or a few hours duration However, it must be remembered that the animal model used herein is not entirely analogous to the human situation Most importantly the infarction in the human cases cited above may not have had an instantaneous onset, and gradually increasing ischemia may have a longer lasting effect in raising threshold especially if the infarction is undergoing the process of extension to involve areas peripheral to the infarcted area Also there are in the human cases other considerations involved in the decision to resect the infarcted area specifically the integrity of postoperative myocardial function Nonetheless the experience of these two surgical groups is compatible with our findings and furthermore it seems probable that the phenomenon observed in the human situation was basically the same as reported for dogs in this report That is, that acute myocardial infarction increases ventricular defibrillation threshold

If the data herein are applicable to man the significance of the increase in threshold which accompanies infarction is not limited to the operating theater since most myocardial infarction occurs outside this area As an extension of our findings, it is reasonable to assume that myocardial infarction would raise the threshold for human trans chest defibrillation of recently (less than two hours) infarcted ventricles This could require about 150 per cent more energy to defibrillate the ventricles and might require up to 435 per cent more energy in individual subjects Since stronger shocks are required for postinfarction defibrillation, it would seem that not only hospitals, but also ambulance coronary care units may require defibrillators with markedly higher electrical output than is presently available This raises the question of what an adequate criterion for electrical energy output would be It has recently been determined in our laboratories that because of inadequate energy and current output commercially available defibrillators cannot consistently defibrillate the ventricles of many animal or human subjects which weigh more than 50 kilograms[2,3] This earlier work indicates that the 300 to 400 watt seconds level of energy usually available should be raised in order to be able to defibrillate the ventricles of a greater percentage of patients The infarction data reinforce this concept. However at the present time there is inadequate information to state with precision the level to which the maximum output of defibrillators should be raised

Summary

The minimum current and energy (threshold values) required for direct ventricular defibrillation in dogs was measured before and after acute myocardial infarction produced by ligation of the interventricular descending branch of the left coronary artery The current waveform employed was a single 8 33 msec duration half sinusoidal pulse Myocardial infarction markedly increased the strength of electric countershock required for ventricular defibrillation in each of the fourteen subjects The average current threshold increase was 55 per cent whereas the average energy threshold increase was 155 per cent The maximum increase in current and energy occurred during the first 30 minutes after infarction and gradually decreased toward control values over the following 90 minutes

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Table I Clinical, laboratory and coronary angiographic findings in 10 patients with left bundle branch block

Patient No.	*Age*	*Sex*	*Clinical history and blood pressure*	*Cholesterol (mg/100 ml.)*	*Chest x-ray*	*Treadmill exercise test*	*Coronary angiogram*	*Final diagnosis*
1	70	M	Angina BP 150/100	265	Minimal LV enlargement	Positive	Not done	Essential hypertension ASHD angina pectoris
2	64	M	Syncope BP 160/80	Not done	Minimal LV enlargement	Positive	Not done	Syncope undetermined etiology ASHD
3	52	F	Angina paroxysmal atrial tachycardia BP 120/80	311 (Type IV)	Normal	Positive	Not done	ASHD paroxysmal atrial tachycardia Type IV hyperlipoproteinemia
4	61	M	Angina BP 120/80	315 (Type IV)	Moderate LV enlargement	Positive	Severe triple vessel disease	ASHD angina pectoris, Type IV hyperlipoproteinemia
5	60	M	Dyspnea on exertion BP 122/76	179	Diffuse interstitial fibrosis otherwise normal	Negative	Not done	Idiopathic diffuse pulmonary fibrosis
6	68	F	Angina pectoris BP 200/90	477	Calcification of right coronary otherwise normal	Negative	Not done	Diabetes mellitus ASHD angina pectoris arteriosclerotic peripheral vascular disease
7	35	M	Atypical angina BP 120/76	157	Normal	Negative	Normal	LBBB
8	40	F	Atypical angina BP 100/70	270	Normal	Negative	Normal	Migraine LBBB
9	31	F	Fatigue BP 130/95	184	Normal	Negative	Normal	Cardiomyopathy LBBB
10	41	M	Angina BP 110/72	312 (Type II)	Normal	Negative	Normal	Paroxysmal atrial tachycardia Type II hyperlipoproteinemia LBBB

LBBB Left bundle branch block
ASHD = Arteriosclerotic heart disease
LV = Left ventricle

and BP) without any prior clinical information The electrocardiographic interpretation was in agreement in all ten patients (Table II)

Five patients had a cardiac catheterization and coronary angiograms which are summarized in Table I

Results

Clinical Five of the patients with LBBB were thought to have classic angina pectoris which was defined as chest discomfort in the sternal area that was provoked by physical activity and relieved by rest. Two additional patients were considered to have atypical angina pectoris in that the chest discomfort was usually but not always associated with activity or relieved by rest Three patients did not have a history of angina pectoris but were evaluated primarily for syncope dyspnea and fatigue which are suggestive of heart disease especially in the presence of LBBB No patient had clinical evidence of congestive heart failure

Electrocardiographic changes All patients had a typical complete LBBB on the resting electrocardiogram The frontal axis ranged from −50 to +60 There was no difference in the frontal axis of the QRS complex in the patients with a positive exercise test as compared to the group with a negative test Patients with a positive exercise test attained an average 91 per cent of the

The diagnostic contribution of exercise testing in left bundle branch block

Jon D Cooksey, M D *
Brent M Parker, M D **
Om P Bahl M D ***
St. Louis Mo

The presence of ST segment and T wave changes in the electrocardiogram of patients with uncomplicated left bundle branch block (LBBB) is expected due to the abnormal direction of the excitation and recovery of the left ventricle [1] These changes are stated to be "secondary" to the altered direction of excitation of the ventricle The ST segment and T wave are usually directed 180° opposite the QRS complex so that an electrocardiographic lead with a predominately positive or upright QRS complex will have an inverted T wave and downward or negative displacement of the ST segment and vice versa in patients with LBBB Since ST segment depression or elevation is the primary criterion for interpreting an exercise electrocardiogram, LBBB is frequently used as an exclusion for exercise testing due to the ST and T changes that are present in the resting tracing [2,3] Others have stated that this left ventricular conduction abnormality does not interfere with the interpretation of the exercise electrocardiogram [4,5] We report our experience with patients having LBBB who have had an exercise electrocardiogram

Method and Materials

From a total of 911 treadmill exercise tests performed from Oct 1971, to May 1973, at Barnes Hospital, ten patients with electrocardiographic findings of LBBB on the resting and exercise electrocardiogram were evaluated LBBB was diagnosed on the basis of the criteria as proposed by the New York Heart Association as follows (1) QRS interval $\geq$ 0 12 seconds and its components are notched and slurred (2) in Leads I and aV_L and leads from the extreme left side of the thorax the initial deflection is usually an R wave which is notched and slurred and (3) the ST segment is most often displaced in a direction opposite to the principal QRS deflection and the T wave usually also points in this direction [6]

The hospital or clinic records of all patients were reviewed for the history and physical findings of cardiovascular disease in addition to that obtained at the time of the stress test (Table I) The four youngest patients were admitted to the hospital specifically to evaluate the LBBB The other six patients were admitted to the medical and gynecological services or seen in the general medicine clinic

A progressive multistage exercise test using the Bruce method was performed on each patient [3] Patients were exercised to 85 to 100 per cent of their predicted maximum heart rate or the test was stopped due to the development of symptoms or significant ST segment changes A modified bipolar V_5 lead with the negative electrode at the upper sternum was used to monitor the electrocardiogram during the exercise test and short strips were recorded at one minute intervals A standard 12 lead electrocardiogram was obtained prior to exercise immediately after exercise and six minutes after exercise The exercise test was read as positive when there was 1 5 mm or greater of flat or downsloping ST segment depression in addition to that present prior to exercise The exercise electrocardiograms were interpreted independently by two of us (JC

From the Departments of Preventive Medicine and Medicine (Cardiovascular Division) Washington University St. Louis Mo
Received for publication Feb 14 1974
Reprint requests Dr J Cooksey Washington University School of Medicine 4556 Scott Ave St. Louis Mo 63110
Assistant Professor of Preventive Medicine and Medicine
Associate Professor of Medicine
Assistant Professor of Medicine

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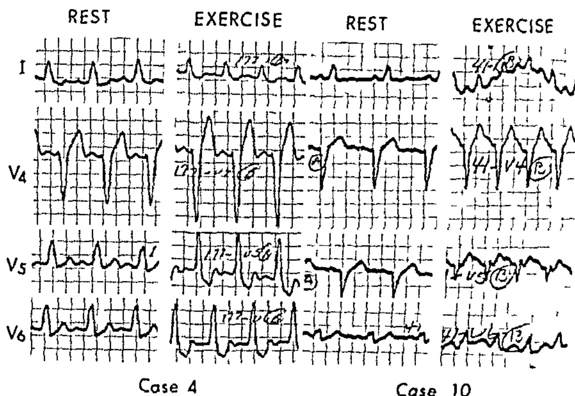


Fig 1 Exercise electrocardiographic tests on two patients with LBBB Case 10 had a normal coronary angio gram while Case 4 showed severe triple vessel disease with 75 to 90 per cent narrowing of the lumen The ST segments were abnormal at rest in both patients and further depression developed during or after exercise Case 4 the patient with severe coronary artery disease shows an additional 4 mm of ST depression while Case 10 a patient with a normal coronary arteriogram shows only an additional 0 5 mm of ST depression

Table II Treadmill exercise test

Patient No	Frontal plane QRS axis	Maximal heart rate		Duration of exercise (min.)	S T segment depression (mm.)		Result	Comments
		beats/min	%		Rest	Exercise		
1	−10	168	100	7	1 00	6 00	Positive	Chest pain
2	+60	175	100	5	1 00	7 00	Positive	Ventricular premature contractions
3	−10	155	91	6	0 25	2 00	Positive	Fatigue dull chest discomfort
4	+25	125	72	3	0 25	3 50	Positive	Chest pain relieved by nitroglycerin
5	−40	165	100	7 5	1 00	0 50	Negative	Fatigue
6	−50	115	72	2	0 75	0 75	Negative	Bilateral hip pain
7	−30	160	87	10	0 25	0 50	Negative	Heart rate achieved
8	0	170	94	4 5	0 75	0 75	Negative	Ataxia
9	0	190	100	5	0 25	0 50	Negative	Fatigue
10	−30	185	100	12	0 25	0 50	Negative	Fatigue

Maximal heart rate % = per cent of predicted maximal heart rate

predicted maximal heart rate while those with a negative test attained 92 per cent of their maximal heart rate There was no difference in the amount of ST depression on the resting electrocardiogram between the positive or negative responders of the treadmill stress test During or following exercise there developed additional ST depression of 0 5 to 7 0 mm The resting and exercise electrocardiogram of a positive and negative responder are shown in Fig 1

Four of the ten patients were considered to have a positive exercise electrocardiogram by the previously described criteria Three of these patients have a history of typical angina pectoris and developed the same discomfort during the exercise test None of the group with a negative

exercise test were noted to develop chest discom fort. Three of the four patients with a positive ex ercise test had mild to moderate cardiomegaly on chest x ray (Cases 2 4 and 6) while cardiac size was normal in the six patients with a negative exercise test

Case 1 was the only patient considered clini cally to have ischemic heart disease and a nega tive exercise test It is probable that this patient had an inadequate amount of exercise in that she walked only two minutes on the treadmill and at tained a maximal heart rate of only 115 beats per minute The six patients with a negative exercise test attained ≥ 85 per cent of their predicted maximal heart rate except for Case 1 who had to stop due to bilateral hip pain

Cardiac catheterization. Of the four patients with a positive exercise electrocardiogram only Case 4 had a cardiac catheterization and coro nary angiography which showed severe obstruc tion (75 to 90 per cent narrowing) of the right coronary left anterior descending and cir cumflex arteries

Four patients (Cases 7 8 9 and 10) with a neg ative exercise test had cardiac catheterization and coronary angiograms Case 7 showed less than 50 per cent narrowing of the distal left an terior descending artery This lesion was not con sidered hemodynamically significant The other three patients showed normal coronary arteries by angiography A moderate elevation of left ventricular end diastolic pressure (LVEDP) was induced with intravenous phenylephrine in Case 9 suggesting myocardial dysfunction The left ventricular function in the other three patients (Cases 7 8 and 10) was considered normal as assessed by the LVEDP and left ventricular angi ogram.

Discussion

LBBB is manifest on the electrocardiogram by an increased duration of the QRS complex and secondary changes in the ST segment and T wave Since the ventricular gradient remains normal in an uncomplicated LBBB the ST seg ment and T wave changes are said to be second ary [7] According to the ventricular gradient con cept, $\hat{A}QRS + \hat{A}T = \hat{G}$ or $\hat{A}T = \hat{G} - \hat{A}QRS$ where $\hat{A}QRS$ equals the area of the QRS complex AT equals the area of the T wave and $\hat{G}$ equals the ventricular gradient [1] In other words every change in the area of the QRS complex causes a corresponding secondary change in the area of the ST T complex which is equal in magnitude but opposite in direction to the change of the QRS It is usually implied that these secondary ST segment and T wave changes associated with LBBB interfere with the interpretation of an ex ercise electrocardiogram [2,3] It would seem that exercise induced tachycardia should not addi tionally change the left ventricular excitation or recovery if the only abnormality was blocked conduction through the left bundle branch and this conduction abnormality was present in a constant fixed manner

The presence of LBBB in asymptomatic pa tients is not rare and many of these are subjected to cardiac catheterization in order to define the etiology of their disease [8] A study of military aviators with LBBB showed exercise testing by means of a Harvard step device to be unreliable in detecting those patients with angiographically documented coronary artery disease [9] On the other hand Master and Rosenfeld[5] have stated that the two step test generally provides valid in formation in patients with LBBB although no figures are given. Feil and Brofman[10] found five out of ten patients with the clinical diagnosis of arteriosclerotic heart disease and LBBB had a positive two step test Lewis and co workers[4] re ported that four patients with LBBB and angiographically documented moderate or se vere coronary artery disease had a positive exer cise electrocardiogram and only one of eight other patients with LBBB and normal coronary arteries had a positive exercise test This excep tion is probably not valid in that the patient was taking digitalis which in itself can cause signifi cant ST changes [11]

We conclude from our study that submaximal treadmill stress testing provides useful informa tion in patients with LBBB The development of an additional 1 5 mm or greater ST segment de pression in the exercise electrocardiogram of pa tients with LBBB is very suggestive of the pres ence of significant coronary artery disease Although a negative treadmill stress test does not exclude significant coronary artery disease our results would seem to indicate that patients with LBBB and normal coronary arteries on an giogram will have a negative test when exercised to more than 85 per cent of their maximal heart rate A negative treadmill stress test in patients with LBBB who are less than 40 years of age

may allow these patients to forgo the expense and risk of coronary angiography

Summary

The significance of ST segment and T wave changes in the exercise electrocardiogram of patients with left bundle branch block is uncertain This study reviews our experience with a graded multistage treadmill exercise test in patients with LBBB The development of additional ST depression of 1 5 mm or greater during or following the exercise test was considered to be an abnormal response Four of the ten patients in the study had an abnormal exercise test Coronary angiography was done in five of the ten patients and agreed with the exercise electrocardiogram These data suggest that the exercise electrocardiogram provides useful diagnostic information in patients with LBBB

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Case reports

Lenegre's disease in a young adult

Ramesh C Dhingra M D*
Ashfaque Khan M D**
J Maurice Pouget M D***
Kenneth M Rosen M D****
Chicago Ill

Two pathological processes have been associated with the development of primary heart block (heart block without other demonstrable organic heart disease) These are Lenegre s disease and Lev s disease[1-3] The former is an idiopathic sclerodegenerative process involving the bundle branches The latter is characterized by similar pathological changes in the bundle branch system but occurs secondary to fibrosis and calcification of the cardiac skeleton related to aging

Antemortem criteria for the diagnosis of both Lenegre s and Lev s diseases are not well defined, but should include (1) development of progressive intraventricular conduction disease eventuating in complete heart block (2) a site of block distal to His bundle and (3) absence of arteriosclerotic heart disease or other demonstrable organic heart disease If an elderly patient fulfills the above criteria Lev s disease would appear to be a reasonable diagnosis[3] If a middle aged or younger individual fulfilled these criteria Lenegre s disease would seem likely[3]

In the present report we describe a patient who had diagnosed left bundle branch block at age 21 and developed complete heart block at the age of 31 His bundle recording revealed a site of block distal to the His bundle suggesting bilateral bundle branch block Review of the literature suggests that this is the youngest reported patient with Lenegre s Disease

Case report

The patient was a 40 year old white man admitted to West Side Veterans Administration Hospital in November 1972 for evaluation of complete heart block. At the age of 21 years (1953) his electrocardiogram revealed left bundle branch block (LBBB) (Fig 1) At the age 31 (1963) 1 degree A V block was diagnosed in addition to LBBB (Fig 2) In the same year he developed 2 1 and intermittent complete A V block (Fig 3) which persisted to the present admission He has been totally asymptomatic There was no prior history of hypertension, angina, rheumatic fever or diabetes mellitus

Physical examination revealed a blood pressure of 130/80 and a pulse of 32 per minute Abnormal cardiac findings included varying intensity of the first heart sound paradoxical splitting of second heart sound, and a Grade II/VI ejection systolic murmur along the left sternal border with no radiation Chest x ray revealed mild cardiomegaly with absence of calcification in the cardiac silhouette confirmed also by fluoroscopy Electrocardiogram demonstrated complete heart block with an idioventricular rate of 33 per minute (Fig 4) Ventricular rates as slow as 20 per minute were observed in the hospital

Hemodynamic and electrophysiological studies Right and left heart catheterization with selective coronary arteriography was performed. Hemodynamic data at rest, after exercise and during ventricular pacing are summarized in Table I Left ventricular end diastolic pressure and pulmonary artery pressures were mildly elevated at rest and during 5

From the Section of Cardiology Department of Medicine Abraham Lincoln School of Medicine of the University of Illinois College of Medicine and the West Side Veterans Administration Hospital.

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Reprint requests to Kenneth M Rosen M.D Cardiology Section, University of Illinois Hospital, P O Box 6998 Chicago Ill 60680

*Attending Physician, West Side Veterans Administration Hospital Assistant Professor Abraham Lincoln School of Medicine University of Illinois College of Medicine Chicago Ill

**Fellow in Cardiology and Instructor in Medicine Abraham Lincoln School of Medicine, University of Illinois College of Medicine Chicago, Ill

***Chief of Cardiology West Side Veterans Administration Hospital Associate Professor Abraham Lincoln School of Medicine University of Illinois College of Medicine Chicago Ill

****Professor of Medicine and Chief Cardiology Section Abraham Lincoln School of Medicine University of Illinois College of Medicine Chicago, Ill

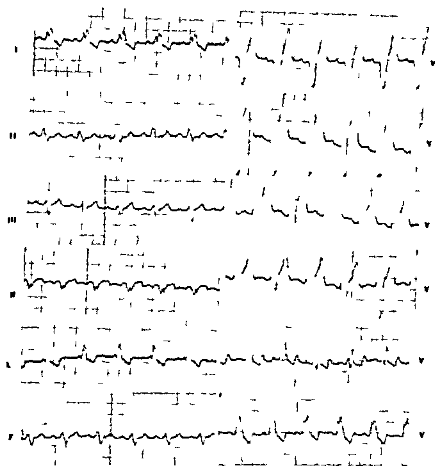


Fig 1 ECG made January 23 1953 Complete left bundle branch block is present. P R interval is 0 14 sec and QRS duration is 0 16 sec

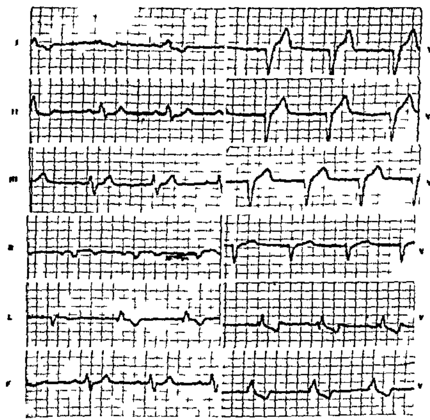


Fig 2 ECG made March 8 1964 1 degree A V block is superimposed on complete left bundle branch block P R interval is now 0 24 sec

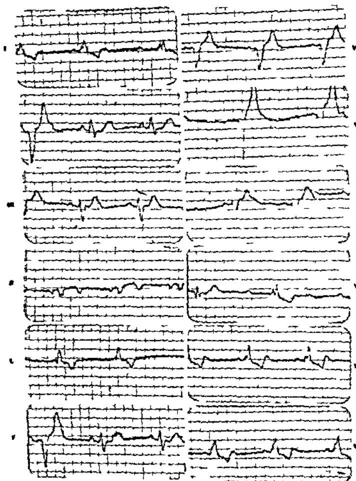


Fig 3 ECG made November 20 1964 2 1 and intermittent complete heart block. The idioventricular rhythm has similar QRS morphology (left bundle branch block)

minutes of alternate leg raising exercise Ventricular pacing normalized these values. Left ventricular end diastolic and end systolic volumes were elevated at rest The basal cardiac output was normal and did not increase during exercise but did increase with ventricular pacing Cineangiogram of left ventricle and selective right and left coronary angiograms were normal.

His bundle (H) electrograms were obtained using previously described techniques.[5] There was complete A V dissociation, with an atrial rate of 81 per minute and a ventricular rate of 30 per minute (Fig 5) Every P wave was followed by an H potential with an A H interval of 85 msec (normal 54 to 130 msec)[5] QRS complexes were wide and were not preceded by H potentials. Thus block was distal to the His bundle recording site (bilateral bundle branch block) A permanent demand ventricular pacemaker was implanted on 11 20/72 The patient has remained asymptomatic and heart size has returned to normal.

Discussion

Lenegre[1] in 1964 reported results of histopathological study in 62 patients with heart block and demonstrated sclerodegenerative lesions involving the bundle branches as the most common finding He noted that the myocardium and the coronary arteries were usually spared. Pathological studies by Davies and Harris[6] in patients with chronic heart block revealed similar findings Rosenbaum and colleagues[3] called this process Lenegre s Disease [3] suggesting that it constituted a definite clinical and pathological entity which could be suspected by observing the progression of bundle branch block to chronic high grade A V block in middle aged patients A similar progression of intraventricular conduction disease in elderly patients could reflect involvement of bundle branches secondary to sclerosis and calcification of the cardiac skeleton (central fibrous body *Pars membranacea*, summit of the muscular septum aortic and mitral valve rings) This process has been termed Lev s Disease [2,3]

The His bundle recording technique has

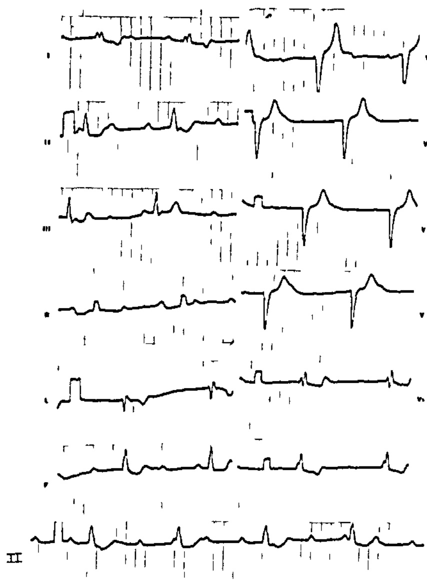


Fig 4 ECG made November 10 1972 Complete heart block with an atrial rate of 88 and ventricular rate of 33 per minute

allowed delineation of the electrophysiological site of block Block may occur proximal to in, or distal to His bundle (H) recording site suggesting respectively A V nodal block, His bundle block, or bilateral bundle branch block [7,12] Patients with Lenegre's disease where there is bilateral bundle branch fibrosis should show a site of block distal to H [13]

In the present patient, LBBB was first noted at the age of 21 years Ten years later PR prolongation also developed probably reflecting additional first degree block in the right bundle branch [14,15] In the same year, the patient developed complete heart block Documentation of the site of block as distal to H suggested bilateral bundle branch block The normal A H interval suggested absence of A V nodal disease

Diagnostic cardiac catheterization did not reveal evidence of either coronary artery disease or valvular disease The increased left ventricular end diastolic pressures and volumes in this patient probably reflected the effects of chronic bradycardia [16,17] Normalization of pressures with pacing supported this conclusion as did the return to normal heart size with permanent pacing

The diagnosis of Lenegre s disease seems reasonable in this patient since there was (1) progression of intraventricular conduction disease eventuating in complete heart block (2) absence of coronary or other demonstrable organic heart disease and (3) a site of block distal to H Review of both pathological cases and of patients reported with complete block distal to H reveals no patient as young as the present reported case[1,2,6,9,11,12,18,19] with the exception of patients

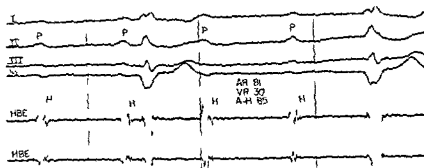


Fig 5 Complete heart block distal to H Shown are ECG Leads 1 2 3 and V_1 and His bundle electrogram (HBE) P is labeled *P* and His potential labeled *H*. Atrial rate (*AR*) is 81 and ventricular rate (*VR*) of 30 per minute Note that every *P* is followed by an *H* potential The QRS complexes are idioventricular and not preceded by *H* potentials

Table I Hemodynamic data at rest exercise and with ventricular pacing

	Rest	*Exercise*	*Ventricular pacing*
Heart rate (beats/min.)	30	,0	65
Left ventricle (mm. Hg)	138/4 20	138/4 23	125/0 5
Pulmonary wedge (mm Hg)	a=26 v=32 $\overline{20}$		
Pulmonary artery (mm Hg)	54/19 ($\overline{26}$)	80/23 ($\overline{35}$)	35/16 ($\overline{22}$)
Cardiac index (liters/M²)	3 0	3 4	5 2
Left ventricle volumes			
EDVI (c c /M ²)	153		
ESVI (c c./M ²)	79		
SVI (c c./M ²)	74		

Abbreviations EDVI = end diastolic volume index ESVI = end systolic volume index, SVI = stroke volume index.

with surgical heart block Thus this patient appears to be the youngest reported patient with Lenegre s disease

The present case thus suggests that the so called benign left bundle branch block in young patients may be an early manifestation of Lenegre s disease [20] Electrophysiological studies in the catheterization laboratory may allow a delineation of those patients likely to develop progressive conduction disease [21,22]

Summary

A patient is reported who had left bundle branch block at age 21 and complete heart block at age 31 Electrophysiological studies revealed complete block distal to the His bundle with normal A H interval, suggesting bilateral bundle branch disease Hemodynamic studies revealed elevated left ventricular (LV) end diastolic pressures which normalized with ventricular pacing, and slight increase of LV volumes Coronary arteriography was normal These findings suggest a diagnosis of Lenegre s disease We believe this to be the youngest reported patient with this diagnosis

This case suggests that benign" left bundle branch block in young adults may be a forerunner of progressive conduction disease Electrophysiological studies in the catheterization laboratory may allow correct diagnosis prior to the development of heart block

We would like to thank Dr Jack Patterson, MC USAF (Scott Air Force Base) who referred this patient to us for evaluation

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Propranolol in the treatment of orthostatic tachycardia associated with orthostatic hypotension

Albert J Miller M D *
Howard C Cohen M D
Gerald Glick M D
Chicago Ill

In their original report on orthostatic hypotension Bradbury and Eggleston[1] emphasized the persistence of a slow heart rate when their patients stood up Subsequently Wagner[2] in his excellent review noted that tachycardia occurred in some patients with orthostatic hypotension and that at times the tachycardia was marked. He explained the tachycardia as compensatory to the hypotension when the cardiac accelerator nerves were spared in the disease process MacLean Allen and Magath[3] described patients with orthostatic tachycardia and orthostatic hypotension and related both phenomena to defects of venous blood return to the heart They reported clinical improvement by conditioning patients with a "head up" bed and the administration of extra salt in the diet Scherba[4] reported a patient with orthostatic tachycardia and orthostatic hypotension and emphasized that this was a disease of the sympathetic nervous system. Treatment with elastic bandages to the legs abdominal binders and ephedrine was ineffective

Wagner[2] stressed that idiopathic orthostatic hypotension is a slowly progressive disease Though various therapeutic interventions have been used with some success in alleviating symptomatology treatment is generally less than satisfactory In the patient presented here the usual types of treatment were not effective in controlling the rather marked orthostatic tachycardia, and this consistent failure in the face of the patient s persistent complaints led us to consider the use of propranolol a potent beta receptor blocking drug That beta adrenergic blocking agents have a marked negative chronotropic effect on the normal heart is well known[5,6] This study was designed to determine the therapeutic efficacy of beta receptor blockade in the setting of orthostatic tachycardia It was hypothesized that slowing of the excessive orthostatic tachycardia would serve to improve cardiac output stabilize arterial pressure and relieve symptoms

Case report

L H a 53 year old Caucasian housewife was referred to the Michael Reese Hospital with the diagnosis of coronary heart disease with angina pectoris. She described frequent left sided chest pain, generalized aching increasing shortness of breath with exertion, and increasing weakness and lighthead dness In addition, she complained of marked palpitations on standing associated with frequent left anterior or retrosternal chest pains Supine blood pressures varied between 110/70 mm Hg and 130/80 mm Hg On standing her blood pressure consistently decreased, falling to levels as low as 75/60 mm Hg Repeated observations revealed that her heart rate rose to as high as 140 beats per minute in the erect posture with her blood pressure after standing 2 minutes varying between 75/60 and 90/70 mm. Hg Treatment with 9 alpha fluorohydrocortisone (0 1 to 0 15 mg daily) was begun and the blood pressures in the erect posture were controlled at levels between 90/70 and 130/80 mm Hg Nevertheless, her standing heart rates continued to increase to 120 to 140 beats per minute and she complained of her heart racing A detailed evaluation, including studies of thyroid and adrenal gland function, revealed no significant abnormalities. She was discharged from the hospital with the diagnosis of orthostatic hypotension and orthostatic tachycardia of undetermined cause Several months later small doses of cortisone were added without any clinical benefit. Retrosternal and left sided chest pains continued to

From the Cardiovascul Institute, M chael Reese Hospital and Medi cal Ce ter Chicago, Ill.

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Reprint requests to Albert J Miller M.D Department of Medicine N rthwestern Memorial Hospital, Wesley P vilion, Superio St. and Fai banks Ct., Chicago, Ill. 60611.

*Present address. Department of Medicine N rthw stern Memorial Hospital, Chicago Ill.

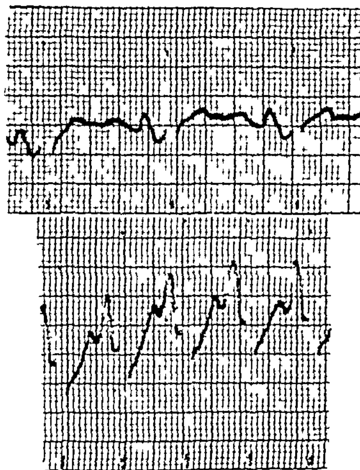


Fig 1 Supine (upper tracing) and standing (lower tracing) ECG of patient The supine heart rate of 68 beats per minute increased to 140 beats per minute with standing changes in ST T contour were associated with the increase in rate

occur with standing and she thought that sublingual nitroglycerin made her feel worse Coronary cineangiography revealed no abnormalities of the coronary arteries

The patient s electrocardiogram showed non specific ST T changes Tachycardia on standing recurred continually (Fig 1) and was associated with retrosternal and left sided chest pains These pains were often relieved by lying down

Because of the persistent and disabling orthostatic tachycardia propranolol 10 mg orally four times a day was started. While taking propranolol her standing blood pressures varied between 90/70 and 120/80 mm Hg and at times her supine blood pressure rose as high as 170/100 mm Hg Her standing heart rates were controlled at 100 beats per minute or less She experienced a feeling of well being and reported that her capacity to be up and about improved markedly to the point that she could be up for as long as four hours with reasonable comfort However because of the development of a generalized maculopapular skin rash the propranolol was discontinued after six months Her tachycardia which had been controlled with propranolol promptly recurred. Treatment with 9 alpha fluorohydrocortisone was continued.

Some six months later at the patient s insistence an attempt was made to re start the propranolol in order to control the persistent and disturbingly rapid standing heart rates that continued to rise to as high as 146 beats per minute A salutary response was again achieved with a dosage of 40 mg daily heart rates on standing not increasing above 100 beats per minute The patient reported feeling better and having improved effort tolerance with less chest pain. However she developed a recurrence of the skin rash in 10 days and the propranolol had to be stopped After discontinuation of propranolol for the second time the standing pulse rates again increased to up to 140 beats per minute

Discussion

In this patient with orthostatic tachycardia associated with moderate orthostatic hypotension the use of 9 alpha fluorohydrocortisone raised the arterial blood pressure, but the tachycardia was not favorably affected Significant improvement in her orthostatic tachycardia resulted from treatment with propranolol on two separate occasions Unfortunately, the use of this drug had to be abandoned because of hypersensitivity reactions

Experience with this patient confirmed our hypothesis that propranolol would slow orthostatic tachycardia just as it does other types of supraventricular tachyarrhythmias It seems probable that treatment with propranolol, by preventing excessively rapid heart rates allowed maintenance of a relatively normal cardiac output and thereby arterial pressure was more easily controlled This concept fits with the hypothesis that idiopathic orthostatic hypotension associated with tachycardia is a disease of the sympathetic nervous system with the sympathetic innervation to the heart remaining relatively intact, while sympathetic tone to the arterial bed is impaired In this patient the beneficial action of propranolol was evident despite the direct and indirect negative inotropic effects that this beta receptor blocking agent exerts on heart muscle Thus it may be concluded that beta receptor blockade has a place in the treatment of orthostatic tachycardia associated with orthostatic hypotension, especially when such tachycardia is refractory to other therapy

Summary

A 53 year old woman developed severe orthostatic tachycardia associated with idiopathic orthostatic hypotension Her standing heart rates up to 140 beats per minute were associated with discomforting palpitation lightheadedness weakness and chest pains, these symptoms persisted with the tachycardia even when the orthostatic hypotension was alleviated somewhat by administration of 9

alpha fluorohydrocortisone Propranolol proved to be effective in slowing the orthostatic tachycardia and the patient s symptoms were markedly alleviated It is concluded that beta blockade has a place in the treatment of orthostatic tachycardia complicating orthostatic hypotension

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Clinical-pathologic conference

John Coon, M D
Leon Resnekov, M D
Chaim Lichtig, M D
Francis Straus II, M D
Chicago, Ill.
With the participation of Eugene E Duda (Radiology)

Clinical abstract This 70 year old Negro male was first admitted to UCHC in October, 1969, because of dyspnea He died 22 months later in August, 1971, during his third hospitalization which was precipitated by developing renal failure and gastrointestinal bleeding

He enjoyed good health until two weeks prior to his first hospitalization when he developed a flu like syndrome with increasing cough and shortness of breath which seemed worse at night. He denied chest pain orthopnea, diaphoresis fever chills or hemoptysis He did note progressive swelling of the legs He had no family history of heart disease, diabetes, or hypertension Past history and review of systems were noncontributory On initial physical examination he was found to be afebrile and in no distress Blood pressure was 120/100, pulse 95, and respirations, 16 Examination of the fundi revealed sharp discs, an A/V ratio of 1 3 and no crossing changes Jugular venous distention was noted at 30° The lungs were clear to auscultation and percussion, except for rare left basilar wet râles The cardiac examination revealed that the PMI was in the sixth intercostal space at the anterior axillary line A grade III/VI harsh ejection systolic murmur was heard at the base and a grade II/VI pansystolic murmur with an intermittant S 3 sound noted at the apex Carotid radial, and femoral pulses were normal Popliteal, dorsalis pedis, and anterior tibialis pulses were not felt Both feet, however, were equally warm and showed evidence of good capillary filling The abdomen was distended The liver was palpable 3 cm below the right costal margin No masses or splenomegaly were detected There was pitting edema from the ankles to the sacrum and scrotum Neurologic examination was within normal limits Laboratory data included white blood count, 7 200 with normal differential, hematocrit, 47% sedimentation rate 2 mm per hour blood glucose 104 mg per cent blood urea nitrogen, 19 mg per cent creatinine 1 4 mg per cent creatinine clearance 49 c c per minute alkaline phosphatase, 55 I U , plasma protein, 5 8 Gm per cent with 2 6 Gm per cent globulin serum cholesterol, 175 mg per cent total serum lipids 456 mg per cent prothrombin time, 12 0/12 4 seconds and uric acid 8 8 mg per 100 ml Serum enzymes were within normal limits Urinalysis revealed 3+ proteinuria and 5 to 10 white blood cells per high power fluid Thyroid function tests were within normal limits Chest x rays revealed cardiomegaly, pulmonary congestion, and bilateral pleural effusions The electrocardiogram showed first degree A V block left axis deviation left atrial enlargement, and probable left ventricular hypertrophy with a possible old anterior myocardial infarction The congestive heart failure was initially treated with bed rest and slow digitalization to which Mercuhydrin Lasix and potassium replacement were later added He improved steadily and lost 18 kilograms of weight. However the underlying cause of his heart condition remained uncertain other than the possibility of cardiomyopathy being present A rectal biopsy was negative for amyloid disease He was discharged on his thirteenth hospital day to continue with Digoxin, 0 25 mg per day, and a low salt diet He remained stable for approximately one year after which he again developed progressive edema and shortness of breath

His second hospitalization was in June of 1971 because of congestive heart failure His blood pressure was 115/90, pulse, 84 per minute respi

From the Departments of Pathology and Medicine University of Chicago Chicago
Received for publication April 8 1974
Reprint requests Dr J Coon Department of Pathology University of Chicago Chicago Ill 60637

rations 20 per minute and temperature 36 6° C He again had edema up to the scrotum and ascites An electrocardiogram now showed sinus rhythm with first degree A V block and changes interpreted as increased left axis deviation old inferior myocardial infarction and old an teroseptal myocardial infarction or fibrosis An intravenous pyelogram showed poor visualization of the collecting systems and a calcification in the right kidney The borderline concentration of the contrast material was interpreted as consistent with the patient s abnormal creatinine clearance The nature of the renal abnormality remained undetermined, but the heart failure was considered secondary to arteriosclerotic car diovascular disease He was treated with an energetic cardiotonic regimen and diuretics and showed slow improvement On his seventeenth hospital day he had a sudden collapse fell to the floor and became comatose He developed a tran sient right hemiparesis that was followed by a brief period of left hemiparesis with complete recovery within one hour He remained other wise stable and was discharged five days later

The last admission was five weeks later because of weakness and color changes in the left foot of two weeks duration He was now found to be cachectic dehydrated and obtunded The blood pressure was 120/80 He was afebrile and not dyspneic. Cardiorespiratory and abdominal findings were unchanged since his last discharge Both legs, however were cold, and the lower 2/3 of the left leg was purple and mottled Carotid, brachial radial and femoral pulses were normal bilaterally as was the right popliteal pulse the left popliteal pulse and both posterior tibialis and dorsalis pedis pulses were not palpable Laborato ry data after rehydration included white blood count, 10 500 with 90 per cent polys hematocrit, 44 per cent sedimentation rate 19 mm per hour urinalysis, normal except for a trace of albumin blood urea nitrogen 37 mg per cent total bilirubin 1 7 mg per cent with 1 3 mg per cent direct serum electrolytes within normal limits and 4+ occult blood in stool. Shortly after admission gangrene of the left leg developed and a week later amputation below the knee was per formed. Surgical pathology confirmed the pres ence of occlusion in several large arteries A sec ond major problem was a persistently low cardiac output. He was initially treated with Isuprel with marked improvement that was not maintained when Isuprel was discontinued The third major complication was recurrent gastrointestinal bleeding thought due to a stress ulcer However several gastric aspirations failed to show any blood. In spite of continued efforts to maintain the cardiac output and the hematocrit at suitable levels he continued to deteriorate Surgery for the gastrointestinal bleeding was ruled out because of his cardiac status He became oliguric the blood urea nitrogen rose to 60 mg per cent, and on his twenty eighth hospital day he died suddenly

Discussion

DR RESNEKOV The patient is a Black male who is 70 years old. From his age we might con sider that we are dealing with hypertensive or coronary heart disease Obviously we should not exclude other important possibilities particu larly cardiomyopathy a disease process involving the myocardium the cause of which remains unknown Our patient was first admitted to this Institution in 1969 with breathlessness no other details are provided Within a period of 22 months the disease process ran its course and he died with renal failure and gastrointestinal bleeding From his history one can deduce that he was in left ventricular failure and that he was having attacks of paroxysmal cardiac dyspnea at night Significantly however he denied chest pain at any time throughout the course of the ill ness Because of progessive swelling of the legs we can assume the disease process affected both ventricles although the right ventricular failure in this man may be secondary to his left ventricu lar failure

The important features on examination shortly after the illness began included elevation of the diastolic blood pressure and a sinus tachy cardia of 95 per minute The appearance of his fundi was against important previous hyperten sion Jugular venous distention was noted. Car diac examination and other confirmatory evi dence suggested enlargement of both ventricles There was a loud pansystolic murmur at the mitral area and a third heart sound was heard. The behavior of the murmur to respirations is not specified, but perhaps with the help of the chest x rays we will be able to surmise that there was tricuspid regurgitation and a separate pan systolic murmur of mitral regurgitation Omi nously the popliteal dorsalis pedis and anterior

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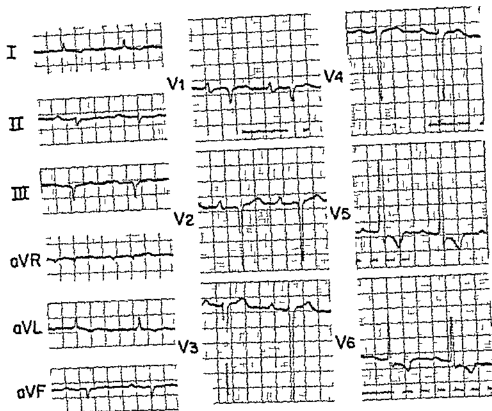


Fig 2 Electrocardiogram showing first degree heart block, marked left axis deviation abnormal P waves and poor R wave progression in frontal leads

infarction The association of these abnormalities might be thought very suspicious of underlying coronary heart disease but cardiomyopathy a disease in which patchy fibrosis occurs in the myocardium could also cause the abnormalities recorded. The patient was diagnosed as being in congestive heart failure appropriate treatment was started, and he responded quickly and well He was discharged from the hospital on the thirteenth day to continue treatment at home and remained well for more than a year

He then had to be hospitalized once more in cardiac failure Apparently the clinical findings were similar on this second admission to those noted before The electrocardiogram now indicated the possibility of additional inferior myocardial infarction An intravenous pyelogram showed poor visualization and a stone in the right kidney He then collapsed suddenly became comatose and developed a transient hemiparesis suggesting either a cerebral embolus or cerebral thrombosis. An embolus could have arisen from an area of endomyocardial thrombosis so common in cardiomyopathy although of course a similar situation may also occur following myocardial infarction Systemic emboli are extremely common in cardiomyopathy as are pulmonary emboli if the disease process also affects the right ventricle A third possible source for a cerebral embolus is the tortuous dilated atheromatous ascending aorta noted on the chest x ray In any case he recovered quickly from the cerebrovascular accident and was discharged home

He had to be readmitted within five weeks because of weakness and color change in the left foot which progressed to gangrene of this foot If this was secondary to a systemic embolus the source once more could well be endomyocardial thrombosis. Because of the gangrene the leg was amputated, but then a second major complication occurred, a persistently low cardiac output. Subsequently renal function deteriorated markedly and he bled from the gastrointestinal tract. He died suddenly presumably in ventricular fibrillation

To summarize this was a 70 year old man in severe right and left ventricular failure He had



Fig 1 Chest radiograph taken in June 1971 demonstrating marked cardiomegaly

tibial pulses were not felt The liver was palpable, possibly due to tricuspid regurgitation and right ventricular failure The neurologic examination was normal

Regarding certain of the laboratory blood investigations the sedimentation rate was low presumably related to his cardiac failure A heavy proteinuria was found This could be due to cardiac failure, but equally might be primary renal disease I think at this point I would like to stop and to have the x rays described as I have no doubt these will be of great help

DR DUDA The first chest film was taken at the time of his first admission in October, 1969 It demonstrated moderate cardiomegaly and bilateral pleural effusion The pulmonary vasculature was engorged and somewhat hazy There was slight bulging of the left atrial appendage and slight elevation of the left main stem bronchus consistent with left atrial enlargement The findings were indicative of congestive heart failure

The second chest film was taken approximately one week later The congestive heart failure has regressed but there is still residual minimal cardiomegaly

The chest film taken in June, 1971, shows that the heart has become much larger, but I cannot identify specific chamber enlargement (Fig 1) The pulmonary vasculature was engorged. The pattern suggests pulmonary venous obstruction There was no pulmonary edema or pleural fluid at this time The rather large heart without frank evidence of heart failure raises the question of a cardiomyopathy or perhaps a pericardial effusion

The first film of the final admission in August, 1971 again demonstrates marked nonspecific cardiomegaly The central vasculature is more engorged and hazy I think the patient has congestive heart failure and probably right subpulmonic effusion The final film, taken in the supine position approximately four weeks later, shows no change in the size of the heart Again there is pulmonary venous engorgement as well as hazy alveolar infiltrates in the right upper and the right lower lung fields The lower infiltrate lies adjacent to the right diaphragm and obscures it This picture is compatible with congestive heart failure but there may be superimposed pneumonia hemorrhage or even infarction

DR RESNEKOV Thank you very much Having seen the chest x rays I am now reasonably certain that the patient did have mitral and tricuspid regurgitation when his heart failure was most severe The abnormal bulge on the left heart border was undoubtedly the enlarged appendix of the left atrium The second x ray taken when he had responded to treatment shows considerable diminution in the overall size of the heart the abnormal left border shadow is no longer present An additional point of diagnostic importance is the specific enlargement of the left ventricle and in addition there is prominence of the ascending aorta and unfolding of the aortic arch

The clinical presentation and chest x ray suggest a disease predominantly affecting the myocardium initially with severe right and left sided cardiac failure with mitral and tricuspid regurgitation We now have to try to determine the cause of the myocardial disease The electrocardiograms show sinus rhythm a first degree heart block, and marked left axis deviation, indeed a left anterior fascicular block (Fig 2) The P waves indicate left atrial hypertrophy The poor R wave progression in frontal leads is suggestive although not diagnostic of myocardial



Fig 6 Electron micrograph of myocardium showing characteristic amyloid fibrils in relation to muscle fibers (top) Tissue prepared from paraffin-embedded block.

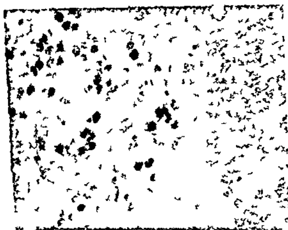


Fig 7 Photomicrograph of left kidney showing recent coagulative infarct on left.



Fig 8 Photomicrograph of lower lobe of right lung showing hemorrhagic infarction

Dr Resnekov in his discussion very properly suggested a cardiomyopathy as the main disease and he was right. There was extensive deposition of hyaline material between the muscle fibers (Fig 5) The Congo Red stain was positive and, when examined under polarized light showed the pathognomonic green birefringence of amyloid Electron microscopy of the heart revealed the characteristic amyloid fibrils (Fig 6) The amyloid deposition is extensive interstitially and shows a few blood vessel walls involved by the process Outside the heart we were able to find amyloid in only a few small vessels of the adrenals submucosa of the jejunum and scattered portal areas in the liver No amyloid was found in the rectal mucosal vessels A small amyloid deposit was found in one of the papillae of the left kidney but no amyloidosis was found in the glomeruli or small renal vessels

As a consequence of this severe myocardial



Fig 3 Markedly enlarged heart weighing 680 grams



Fig 4 Opened heart showing left ventricular hypertrophy and thrombus in left atrial appendage (arrow)

mitral and tricuspid regurgitation and an elec trocardiogram compatible with either coronary heart disease or cardiomyopathy His disease was complicated by episodes of systemic embolism He eventually died suddenly in low cardiac out put and uremia I am impressed by the predomi nant presentation here of myocardial failure first, followed by episodes of systemic embolism Pulmonary emboli were probably found at autop



Fig 5 Photomicrograph of left ventricular myocardium showing extensive deposition of amyloid between the muscle fibers.

sy My primary diagnosis is cardiomyopathy The most likely cause of this in a man of 70 years is amyloid disease My clinical diagnosis therefore is amyloid disease, cardiomyopathy, endomyocar dial thrombosis, systemic emboli, biventricular failure, mitral and tricuspid regurgitation patchy fibrosis of the myocardium with first degree heart block, and left anterior fascicular block, death ultimately being caused by ventricu lar fibrillation during a low cardiac output state and uremia

DR LICHTIG Starting with the examination of the amputated leg and the rectal biopsy, the posterior tibial artery showed an old organized thrombus The popliteal artery showed thicken ing of the wall and a freshly organizing throm boembolus The other arteries showed a moder ate degree of atherosclerosis. These findings of organized thrombi and atherosclerosis explain the two year story of poor pulsation in his legs. The recent embolus in the popliteal artery is responsible for the left leg gangrene

At autopsy there were 500 c c of clear ascitic fluid and bilateral pleural effusions The heart was greatly enlarged weighing 680 grams (Fig 3) All chambers were dilated and hypertrophied There were old organized thrombi in the right and left atrial appendages (Fig 4) Sections through the myocardium revealed no old infarc tions or diffuse fibrosis The heart valves were unremarkable The coronary arteries showed only slight atherosclerosis with no occlusion old or fresh

Fundamentals of clinical cardiology

Changing views on the mechanism of the first and second heart sounds

Aldo A Luisada M D F A C P
Donald M MacCanon Ph D
Sudarshan Kumar M B B S M R C P , F R C P (C)
Larry P Feigen Ph D
Oak Forest, Ill.

One can trace the origin of a commonly held view on the mechanism of the heart sounds to that accepted a long time ago by the British Medical Society on the basis of the proposals of appointed committees. These established that the first sound is due to the combined vibrations of the contracting ventricles and auriculoventricular valves and possibly also the semilunar valves that the second sound is entirely due to vibrations of the closing semilunars "[1]

Since that time two divergent concepts have developed. the first was propounded by most physiologists (Ceradini[2] Luciani[3] Wiggers [1] and Rushmer[4]) who de emphasized the part played by the cardiac valves, while the second was strongly supported by clinical cardiologists (Leatham[5] and Dock[6]) contending that either valve closure or valve tension was the *only* cause of the heart sounds On the basis of work done in our laboratory and by other investigations conducted elsewhere most physiologic and clinical observations strongly support the former view

It is the purpose of this presentation to restate these facts for wider appreciation recognition of which can only prevent the establishment of a dogma and encourage further research in one of the most fascinating fields of cardiology

First sound

Time events in relation to pressure changes Di Bartolo and co workers[7] showed in our laboratory that both atrioventricular (A V) valves are completely closed at the time of the first rapid vibration of the first sound. This was demonstrated by the fact that the crossing points of the atrial and ventricular pressures of both sides of the heart preceded the onset of the first high frequency vibration (mitral component) of the first sound by an interval of 20 to 25 msec * It is obvious that, when the pressure rises in a ventricle while it is either stable or dropping in the respective atrium the valve separating them has already completed its closure and acts as a barrier preventing pressure rise in the atrium These findings were further confirmed in animals by van Bogaert and co workers[8] von Egidy,[9] and Laurens [10] as well as in our clinical catheterization laboratory[11,12] on the basis of pressure and sound tracings In order to prevent catheter delay effects on the recorded waves subsequent studies performed in our laboratory with catheter tip sensors, further confirmed the above observations (Fig 1) [13] Other studies performed with various techniques led to the *same conclusions* They include (1) observations made in man and dog by means of routine angiocar*diography*[14] and routine or very high speed cineangiocardiography[15] and (2) observations

From the Departm t of Physiology nd Med cine of Th Ch cago Medical School-Uni ersity of Health Sciences, the Department of Cardiology Oak Forest Hosp tal, the School of Public Health, University of Illinois, a d the Department of Cardiology North western Uni ersity School of Medicine

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Reprint requests: Dr A. A Luisada Department f Cardiology Oak Forest Hospital, Oak Forest, Ill 604 2.

*The value f the crossing point of two pressure tracings has been discussed, and it has been stated that it may not represent val e closure While this may be true in the case of the semilunar val es where the momentum of flow may maintain the val e open for a brief interval (see later-second sound) it is *not* applicabl to the mitral valve In this case forw rd flow would be folowed by backward flow if the valve were incompl tely closed.

amyloidosis, he developed congestive heart failure and pleural effusion The liver shows severe chronic passive congestion

As Dr Resnekov pointed out, multiple emboli are very common in cases of cardiomyopathy, and we found organizing and fresh infarcts in both kidneys (Fig 7) in addition to the embolus found in the amputated leg The history of transient hemiparesis can be explained by an embolus to the posterior cerebral artery The hippocampus and lingual giruses showed organizing infarctions These lesions are compatible with a two month old brain infarction as suggested by the clinical history There were also pulmonary emboli with a right lower lobe hemorrhagic infarction (Fig 8)

The cause of his gastrointestinal bleeding is not clear The only possible bleeding source was a number of small shallow ulcerations in the mucosa of the anus and rectum These small ulcers seem an unlikely source for the patient's extensive gastrointestinal bleeding A rather unexpected finding was a moderate acute pancreatitis Acute pancreatitis is not a rare finding in cases of severe congestive heart failure

The finding of heart involvement in amyloidosis is certainly not a rare one Cohen[1] in his series of 42 cases of amyloidosis found clinical cardiac disease in 80 per cent of those with primary amyloidosis those with myeloma had a 90 per cent incidence and those with secondary amyloidosis had an incidence of 60 per cent The incidence of cardiac involvement in amyloidosis increases with age and is slightly higher in females There was no evidence for any condition underlying the amyloidosis such as multiple myeloma, any chronic inflammatory disease, or malignancy

The cause of death was probably an arrhythmia

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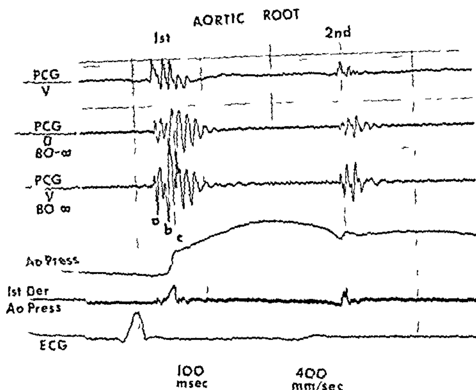


Fig 2. Tracing of aortic pressure (Ao Press) close to the aortic valve and external phonocardiograms in the same dog as in Fig 1 The pressure tracing was recorded by a catheter tip pressure recorder The third phonocardiogram from above is a velocity tracing with sharp filtration (48 db per octave) of the vibrations below 80 Hz. The second and third are high pass tracings with nominal frequency at 80 Hz Three components are visible in this tracing When the electronic delay for this tracing (5 msec) is deducted, the onset of component b coincides with the onset of rise in pressure in the aortic root indicating its coincidence with aortic valve opening D = displacement Der = derivative V = velocity (From Luisada and co-workers Am J Cardiol 1971 Courtesy of the Journal.)

mitral valve However the latter still slightly precedes the onset of the first sound as proved by both pressure and echocardiographic tracings

Temporal relation of A V valves closures In man tricuspid valve closure slightly follows mitral valve closure in the anesthetized dog it may slightly precede or slightly follow it but is frequently simultaneous Di Bartolo and coworkers[7] found a 29 msec. average interval between the onset of the Q wave of the electrocardiogram (ECG) and the completion of mitral valve closure and a 34 msec average interval between the Q wave and tricuspid valve closure More recently using catheter tip sensors, we have found intervals of 25 and 35 msec. respectively[11] Both studies were performed in dogs anesthetized with pentobarbital In man we found average intervals of 26 6 msec. for the Q mitral closure interval and 44 1 msec for the Q tricuspid closure interval.[23]

Components of the first heart sound Traditionally only two components of the first heart sound have been recognized and have been attributed to mitral and tricuspid valve closure by Leatham[5] However data obtained in our laboratory[13,24] strongly suggest that the first heart sound is usually formed by *three groups of high frequency vibrations or components* The first component follows completion of mitral closure by 20 to 25 msec.* The second component occurs from 30 to 45 msec after the first and, as shown by studies in our laboratory[13] coincides with the end of the isovolumic period and the opening of the aortic valve (Fig 2) The third component (when present) occurs at the point in which the

*Rushmer[4] starts the description of the first heart sound with a slow vibration that he calls component 1 (we have called it 0 component) Thus the first high frequency component that we call a is equivalent to his component 2 while our second high frequency component b is equivalent to his component 3.

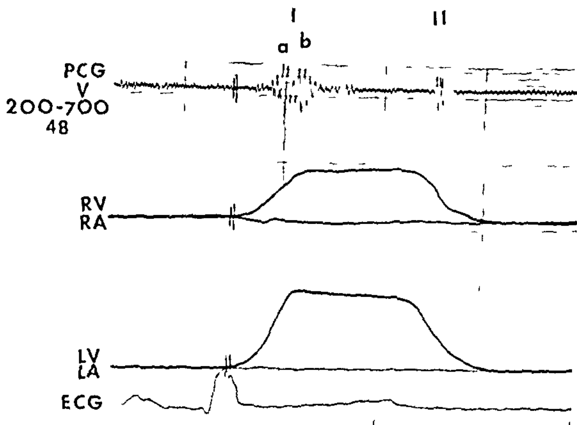


Fig 1 Experiment in a dog demonstrating the time of atrioventricular valves closures and the time of onset of the first heart sound RV RA and LV LA crossing points are nearly simultaneous and are marked by pencil signals Pressure tracings recorded with catheter tip and subminiature pressure gauges with insignificant time delay RV and RA tracings ×2 LV and LA tracings ×5 The upper tracing is an external velocity phonocardiogram in the high frequency band 200 to 700 Hz (electronic delay 10 msec) recorded at the point of maximal impulse After correction the interval between crossing and onset of high frequency vibrations of the first heart sound is 29 msec Times lines 100 msec film speed 400 mm per second ECG = electrocardiogram LA = left atrium LV = left ventricle PCG = phonocardiogram RA = right atrium RV = right ventricle V = velocity Note the splitting of the first sound in spite of simultaneous closure of the A V valves (From Luisada and co workers Am J Cardiol 1971 Courtesy of the Journal)

made with ultrasound equipment using the Doppler effect[16] or with echocardiography of the anterior leaflet of the mitral valve (Figs 2, and 10) *[17 19]

Thus, it would seem that in sinus rhythm relaxation of the left atrial musculature is accompanied by gradual closure of the mitral valve *prior to left ventricular contraction* as also stated by Sarnoff, Gilmore and Mitchell [20] This closure is a relatively *slow movement*, and (on the basis of our echocardiograms of the anterior mitral leaflet) lasts about 40 msec Apposition of the leaflets is *strengthened* by the subsequent elevation *of pressure within the left ventricle while* excessive elevation is prevented by contraction of the papillary muscles which according to Armour and Randall [21] follows shortly that *of the* anterobasal musculature as well as the ventricular pressure rise This basic concept had been already reported by Luciani[3] over 60 years ago as a result of his experiments

Furthermore, Hamby Aintadlian and Wisoss[22] made the interesting observation that, with sinus rhythm even prosthetic *ball valves* close *before* left ventricular contraction in spite of the abnormal atrioventricular pressure gradient that is invariably present in this situation

In atrial fibrillation or A V block the effect of a coordinated atrial relaxation is not involved Then pressure rise caused by left ventricular contraction is the main cause of closure of the

* Observation of an echocardiogram of the anterior leaflet (Fig 10) reveals that, *following the anterior motion (opening) caused by atrial contraction* (wave A) the leaflet mov s posteriouly (closing) during atrial relaxation (A B) When ventricular *contraction starts a further* posterior movement occurs this may be minor or significant according to the individual case Such a movement can be considered as caused by (1) upward motion of the entire heart, and (2) mitral valve lift *caused by increased ventricular pressure acting on a closed mitral valve This point* B occurs slightly before the first high frequency component of the first heart sound

These studies fail to prove any contribution of the normal right ventricle to the first sound

If one wishes to speculate on the reasons for this lack of contribution of the right ventricle which was further established even in cases of right ventricular hypertrophy the following considerations can be advanced (1) the right ventricle has a semilunar shape in contrast with the left, which is an ovoid (2) except for conditions of hypertension the right ventricle causes only a small rise of pressure (3) its outflow tract normally contracts from 25 to 50 msec after the inflow tract[30] so that vibrations caused by inflow tract contraction would be dampened by the relaxed state of the rest of the ventricle, and (4) due to the lack of significant asynchronism if there are small vibrations they are superimposed on those of the left side (This however does not apply to cases of LBBB where a more distinct separation should occur)

Mitral valve tension and first sound Would *tension* of the mitral valve cause or contribute to the sound energy of this sound, as stated by Dock?[31] It should be remembered that the energy of any sound caused by a force acting on a structure is proportional to the product of the mass of the structure the acceleration imparted to the latter and the distance traveled by it. Physical properties of the valve and of the cardiohemic system as well as their interrelationship make the effect of tension unlikely because of (1) similar specific gravity of valve and blood (in contrast with examples of violin cords snapping sails and closing doors) (2) lack of an efficient resonant chamber and (3) inadequate weight and motion

To clarify this problem MacCanon and co workers[15] studied the parameters of energy of the first sound in the dog They analyzed (1) the sound energy of the first sound (2) the linear motion of the mitral valve interface and (3) the weight of the mitral valve with its chordae Assuming conditions most favorable to energy production by the valve their calculations showed that mitral valve tension alone cannot account for more than 10 per cent of the total sound energy while the rest is accounted for by the *entire* cardiac and hematic mass of the left ventricle On the basis of this information valve tension cannot be accepted as a significant contributory factor in the production of the first sound.

Left ventricle and first sound A comparison of

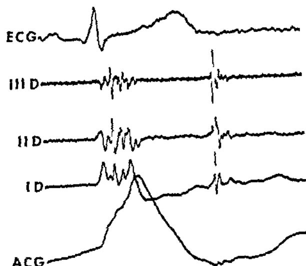


Fig 4 Tracing recorded with a single contact microphone placed at the apex in an 18 year-old normal male From below apex cardiogram (ACG) first derivation of the ACG (dp/dt) second derivative of the ACG (d^2p/dt^2) third derivation of the ACG (d^3p/dt^3) Speed 200 mm per second—time lines 40 msec Note the gradual transformation of the apex cardiogram into a phonocardiogram by the use of the derivatives a process that is similar to a filtering technique (From Luisada and co workers Jap Heart J 14 406 1973 Courtesy of the Journal.)

the early systolic wave of the first derivative (dp/dt) of left ventricular pressure with the first sound has shown that both exhibit similar changes in amplitude under (1) the influence of cardiomimetic drugs (2) ventricular overload or (3) as a result of experimental myocardial infarct[32] This early systolic wave shows several small ripples or oscillations that coincide with the main components of the first heart sound[24]

The amplitude of this systolic wave varies similarly to that of the first sound under the influence of drugs or surgical procedures*[32,33] this correlation is also found in alternans[34] and in atrial fibrillation[35] and has been accepted for cases of A V block[36] The special alterations of dynamics occurring in mitral stenosis are the cause of the typical increase and delay of the first sound, as discussed by Kurz Slodki and Luisada[37] and Chaillet[38] and are revealed by the dp/dt of left ventricular pressure[37]

Recent experiments in our laboratory[40] indi

An even close approximation is to be expected in future studies comparing the first sound recorded on th chest wall and the early systolic vibrations of the th d deri ati e of left ventricular pressure under arious conditions 40

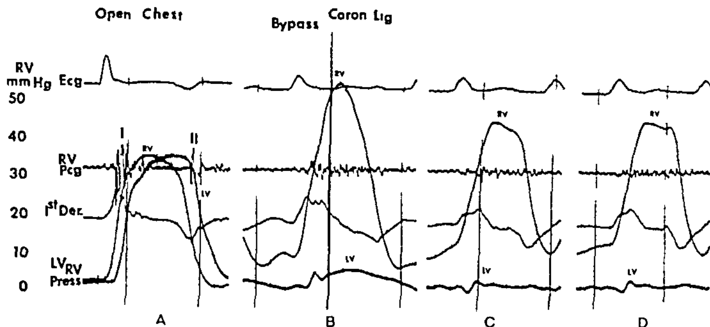


Fig 3 *A* Records with open chest from an experimental dog Right ventricular pressure and phonocardiogram are recorded with a Dallons Telco micromanometer placed in the center of the right ventricle The first derivative of the right ventricular pressure is obtained through an analog computer circuit. Left ventricular pressure is recorded by means of a catheter introduced in the left ventricle through an apical puncture and a Statham strain gauge Amplification of left ventricular pressure is ¼ of that of the right ventricle (the apparent delay between the two pressure curves is due to catheter delay in the case of the left ventricle) *B* Records obtained after left heart bypass and ligature of the circumflex branch of left coronary artery Marked reduction in the amplitude of the heart sounds of the right ventricle *C* Records obtained after withdrawing of residual blood from the left ventricle *D* Records obtained after opening the cavity of the left ventricle Complete disappearance of the heart sounds in the right ventricle (From Luisada and co workers J Appl Physiol 1968 Courtesy of the Journal)

still rising aortic pressure curve shows a change in slope (Fig 2)

The interval between completion of mitral and tricuspid valve closures is very short in man averaging 17 5 msec [23] This fact the short interval existing between tricuspid valve closure and onset of the second component of the first sound and the coincidence between this component and aortic valve opening suggest that *the second component is not related in any way to the closure of the tricuspid valve* [13]

Further clinical confirmation of this fact can be obtained in patients with bundle branch block (BBB) [25] While those with RBBB have a first sound with three normal components those with LBBB have a small first sound that is delayed over the onset of the RS complex of the ECG [25] A similar phenomenon can be found both in right ventricular paced beats and right ventricular ectopic beats [26] Should there be a tricuspid component, this would have a normal amplitude and a normal relationship to the onset of the RS complex in LBBB Claims about a large ' tricuspid component in atrial septal defect again were not substantiated by our observations[27] or those of Plass Schmidt and Guenther[6] because that component occurred too late for being related to tricuspid valve motion Thus the large vibration that can be recorded in some of the cases may be either a large *b* component or an ejection sound. '

Role of the two ventricles in the production of the first sound Intraventricular sounds were recorded by catheter tip probes within the two ventricles in dogs in order to evaluate the part played by each ventricle The right ventricle exhibited vibrations that were simultaneous with those of the left ventricle though much smaller Experiments were then performed in our laboratory by excluding one half of the heart *from the circulation* Bypassing of the right heart caused *no change* in the duration and pattern of the first sound recorded within the left ventricle [28] Bypassing of the left heart plus ligation of the circumflex branch of the left coronary artery caused *complete disappearance* of the first sound within the right ventricle in spite of a moderate pressure increase in this chamber (Fig 3) [29]

between the respective vessel and ventricle created by the sharp decline of intraventricular pressure

Subsequent studies by means of angiocardiography showed that the momentum of blood flowing from each ventricle into its artery maintained the leaflets open for a brief interval after the initial divergence of the aortic and left ventricular pressure curves Spencer and Greiss[48] stated that at the moment in which blood flow reverses its course in the ascending aorta the aortic pressure pulse begins its sharp drop which then becomes the incisura At this moment back flow abruptly ceases and the aortic pulse rises again as a rebound wave Studies by Mac Canon Arevalo and Meyer[49] with a specially made electric device introduced into the aortic valve have demonstrated that this valve closed slightly *after* the end of ventricular contraction (Fig 5) The interval between the end of ventricular contraction and aortic valve closure is very short in the normal heart (in the range of 8 to 10 msec. in the dog[49] up to 15 msec in man[22]) and is probably due to the momentum of the forward flowing blood. It seems appropriate to call this interval the "inertial interval It is grossly similar to the so called protodiastole of Wiggers, except that the latter was considered to end with the incisura

The aortic component of the second sound occurs 8 to 15 msec. *after valve closure* at the time of the incisura of the aortic pressure pulse recorded near the aortic valve.

In their studies of blood ejection and pressure gradient across the pulmonary valve Okino and Spencer[50] obtained findings similar to those observed across the aortic valve

More recently Brough and Talley[51] concluded that the onset of the aortic component of the second sound occurs in the dog 5 2 msec (± 2 6) before the nadir of *flow* reversal and 23 2 msec (± 5 7) after the onset of rapid deceleration of flow This study confirms those of Mori and co workers[52] and Kusukawa and co workers[53] in our laboratory The latter studied the pressure differential across the aortic valve and its first derivative

While the inertial interval in the two arteries is similar so that closure of the aortic and pulmonary valves occur approximately at the same time the interval separating each valve closure from the respective sound component is longer for the right than for the left side of the

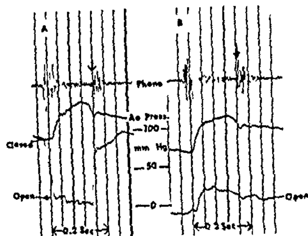


Fig 5 Tracings recorded in a dog with an electric contact revealing the closure of the aortic valve (The beginning of rise of the contact tracing had been shown in controls to be evidence of complete closure) *A* From above phonocardiogram aortic pressure tracing contact tracing *B* The same after contactor device had been withdrawn from aortic valve into ascending aorta (From MacCanon and co workers Circ Res 14:387 1964 Courtesy of the authors and the Journal)

heart[54] This fact probably due to the greater compliance of the pulmonary vessels causes a more delayed rebound over the closed valve so that both a late pulmonary incisura and a *late* pulmonary component of the second sound will occur Inspiration and expiration are accompanied by minimal changes in the duration of ventricular systoles while marked changes in the interval between aortic and pulmonic incisuras as well as changes in the interval between aortic and pulmonary components of the second heart sound, are observed These changes seem to be caused primarily by the increase in capacity of the pulmonary vessels so that the pulmonary artery takes longer to reach its elastic limits and thus delays the rebound of its pressure pulse

In conclusion there are three successive events for each side (1) end of ventricular contraction (2) valve closure and (3) incisura in the flow and pressure curves accompanied by the respective sound component (aortic or pulmonic) (Fig 6) *

Abnormal second sound It is clear from the previous description that the second sound may present three different abnormal aspects (1)

* One might suggest that the sound component is equivalent to the third derivative of the pressure pulse at the time of the incisura or in other words, represents the high frequency components of this sudden change in pressure and flow

cate that a left ventricular pressure tracing contains all the essential parts of a phonocardiogram, differentiation (third or higher derivative of pressure) or filtration (high pass filter at 50 Hz or higher with 48 db per octave slope) transforms the pressure curve so that it becomes identical to a phonocardiogram recorded in a medium or high frequency band A similar striking result can be obtained through filtration or differentiation of the apex cardiogram (Fig 4)

We have finally come to the realization that the first sound is simply the manifestation of the high frequency components of the pressure induced vibrations of the left ventricle Our process of differentiation or filtration of intracardiac vibrations mimics the effects of transmission through tissues plus filtration as used in the taking of a phonocardiogram It should be recalled that 'sonic vibrations' had been previously identified in the blood of cardiac chambers by studies in our laboratory[41] were studied by several investigators[41-44] and have been correlated with the dynamic events of the left heart and aorta[45] This concept explains the frequency distribution of the heart sounds on the chest in normal subjects[46] which is somewhat different from that empirically described by the clinicians of the last century

Conclusion At this point the following pertinent conclusions can be drawn in regard to the first sound (1) it is a long series of sound vibrations which occur in early systole *after* closure of the A V valves (2) these are caused by contraction of the left ventricle and are grossly proportional to the rapidity of the pressure rise in this chamber, (3) contribution of mitral valve tension to this sound is minimal and (4) the various groups of vibrations of this sound are present in the pressure tracing of the left ventricular chamber

Possible mechanism of production of the first sound If one looks at the possible causes of the first heart sound the most likely explanation is that advanced by Rushmer who suggested that the "vibrations of the cardiohemic system" (heart sounds[4]) were caused by acceleration and deceleration of the blood (The terms acceleration and deceleration" should be viewed as representing active forces which may be manifested as either changes in pressure or actual physical displacement of tissue) In an elastic chamber filled with fluid any sudden motion throws the whole system into vibration the momentum of the fluid causes stretching of certain portions, followed by a recoil and a displacement of fluid in the opposite direction The rise in left ventricular pressure may be regarded as a manifestation of a contractile force which, except for a resistance offered would have accelerated the blood into the aorta Prevented from doing this by the closed valves the left intraventricular blood mass is instantaneously decelerated Thus the contractile energy tending to accelerate the blood is converted into the potential energy of pressure during isovolumic contraction

The power source resides in the left ventricular mass the elastic structures that "give in" for a brief time are the base of the left ventricle and the mitral valve The vibrations arise in the left ventricular wall the septum, the blood of the left ventricle and the mitral valve each section contributing in proportion to its movement and its mass The opening of the aortic valve causes a sudden kinetic acceleration of the blood, and thus can be responsible for separate vibrations

It should be kept in mind that older theories explaining the first sound as caused by the muscular contraction were based on the observation that a vibrant hum can be recorded on a skeletal muscle contracting tetanically, and were found to be in error Were this theory true the first sound would last throughout systole On the other hand, experiments denying that the ventricular wall can cause sonic vibrations were based on studies made with flaccid relaxed tissue and not with a contracting muscle[6]

Second sound As shown by Leatham[5] normally there are two components of the second sound the *aortic* and the *pulmonary* which follow each other in this order The interval between them is greatest at the end of inspiration or soon afterwards, and smallest at the end of expiration

The possibility of a more complex appearance of the aortic component has been studied by Luisada and Argano[47]

Hemodynamic correlates Ceradini[2] first stated that the semilunar valves are maintained by the aortic flow in a semi opened position so that eddies form in the sinuses of Valsalva As soon as flow decreases these eddies approximate the leaflets Luciani[3] and then Wiggers[1] confirmed this fact following animal experiments According to them the semilunar valves close at the onset of diastole due to the pressure difference

between the respective vessel and ventricle created by the sharp decline of intraventricular pressure

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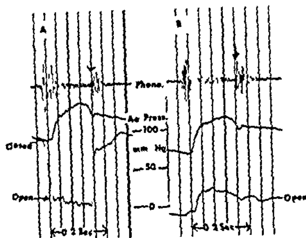


Fig 5 Tracings recorded in a dog with an electric contact revealing the closure of the aortic valve (The beginning of rise of the contact tracing had been shown in controls to be evidence of complete closure) *A*, From above phonocardiogram aortic pressure tracing contact tracing *B*, The same after contactor device had been withdrawn from aortic valve into ascending aorta (From MacCanon and co-workers Circ Res. 14 367 1964 Courtesy of the authors and the *Journal*)

heart.[54] This fact probably due to the greater compliance of the pulmonary vessels causes a more delayed rebound over the closed valve so that both a late pulmonary incisura and a late pulmonary component of the second sound will occur Inspiration and expiration are accompanied by minimal changes in the duration of ventricular systoles while marked changes in the interval between aortic and pulmonic incisuras as well as changes in the interval between aortic and pulmonary components of the second heart sound, are observed. These changes seem to be caused primarily by the increase in capacity of the pulmonary vessels so that the pulmonary artery takes longer to reach its elastic limits and thus delays the rebound of its pressure pulse

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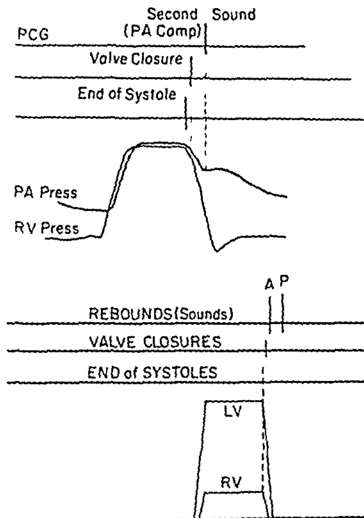


Fig 6 *Top* Scheme of time relationship of the end of right ventricular systole semilunar valve closure and pulmonary component of second sound *Bottom*, Scheme of the relationship between right and left ventricular systoles semilunar valve closures and components of second sound. (*Bottom figure* is from Luisada Am J Cardiol 1971 *Top* is from Luisada The Sounds of the Diseased Heart St Louis 1973 W Green Courtesy of the publisher)

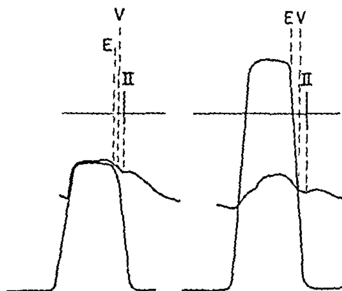


Fig 7 Schematic comparison of the left ventricular and aortic pressure curves with the phonocardiogram. *Left*, normal heart. *Right* heart with aortic valve stenosis. E = end of left ventricular systole V = aortic valve closure II = aortic component of second heart sound Note delay between E and V and greater delay of II over V in aortic stenosis (From Kumar and Luisada Am J Cardiol., 1971 Courtesy of the Journal)

wide splitting of the normal type (in certain conditions this is also manifested by fixed splitting) (2) single second sound and (3) reverse splitting

It is obvious that changes of the dynamics of either ventricle and either artery may be involved in the appearance of these three types

Delayed ventricular activation causes a delayed beginning and, therefore, a delayed ending of ventricular contraction This mechanism has been accepted for a long time as the cause of wide splitting of the normal type occurring both in RBBB and in left ventricular ectopic or paced beats the delay in right ventricular dynamics causes a delayed occurrence of the pulmonary component Studies of Luisada, Kumar, and Pouget[55] have shown that the same mechanism applies to LBBB (in addition to other factors—see below), in which delayed occurrence of the aortic component results in reverse splitting

Prolongation of the isovolumic contraction period causes delayed semilunar valve closure unless compensated by abbreviation of the ejection period Prolongation of this period for the left ventricle is typical of cardiomyopathies and may occur in coronary heart disease and possibly in left ventricular failure This may be an additional factor of reverse splitting in LBBB

Prolonged ejection due to a dynamic mechanism, is present in semilunar valve stenosis The semilunar valve will not close until the ventricular pressure has reached the low level of the arterial pressure This mechanism must operate in pulmonary valve stenosis (wide splitting of the normal type) and has been demonstrated in aortic valve stenosis (either close or reverse splitting) by Kumar and Luisada (Fig 7)[56] An additional element (see below) is related to poststenotic dilation of the main artery which further delays the incisura

Delayed rebound over the closed semilunar valve may occur as a result of peripheral phenomena mostly related to increased flow It is typically found in atrial septal defect[57] (Fig 8) and is probably the cause of the wide splitting of

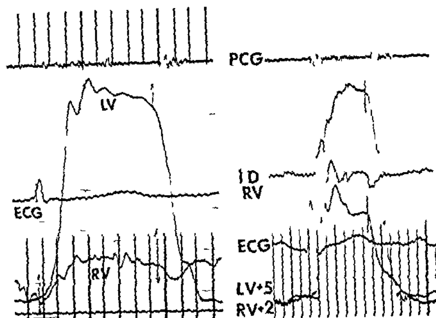


Fig 8 *Left*, Normal 53 year-old male Right and left ventricular pressure tracings recorded at catheterization (both × 5) Very close onset of pressure rise in the two ventricles Simultaneous end of systole *Right* External phonocardiograms and pressure tracings at catheterization in a case of atrial septal defect (sep um secundum type) Comparison of phonocardiogram with first derivative of right ventricular pressure electrocardiogram and pressures of the two ventricles. Right ventricular pressure is more amplified than left ventricular pressure (×2 vs ×5) Both ventricles initiate and terminate their contraction as in normal subjects. (*Right* is from Kumar and Luisada Am J Cardiol. 1971 Courtesy of the Journal)

the normal type that is found in this condition Dilatation of one of the main arteries (most ac centuated in the case of the pulmonary artery) is a common result of increased flow this can be a contributory element of delay of a component but can be the only cause if it results from intrinsic changes of the wall.[58]

Some degree of retrograde flow at the beginning of right ventricular diastole occurs in severe pulmonary hypertension it causes a *slower drop* of right ventricular pressure and a *delayed* closure of the pulmonary valve [59] This brief phase of bidirectional flow explains the *wide splitting* that is found in both acute and chronic pulmo nary hypertensions

The above considerations have been recently presented in greater detail taking into account several other clinical conditions [60]

It is therefore concluded that changes of ac tivation or contraction of each ventricle as well as dynamic and peripheral factors influence the timing of the aortic or pulmonary incisura thus affecting the type of splitting of the second sound.

The most unusual situation is that occurring in severe pulmonary hypertension which exhibits a behavior of the pulmonary component that seems at first to contradict what is generally oc curing in cases with mild pulmonary or aortic hy pertension

General considerations

The conclusions to be drawn from the studies of the last decade are the following The car diovascular system contains three power sources causing sounds the left ventricle the aorta and the pulmonary artery

1 In the case of the left ventricle the power resides in the left ventricular musculature that tends to accelerate blood while this is prevented by the closed valves The vibrant mass includes the free wall the septum, the mitral value and the blood contained in the ventricular chamber Following the first vibration both the opening of the aortic valve (by starting a new phase of ac celeration) and the initial tension of the aortic wall add sound components thus adding to the

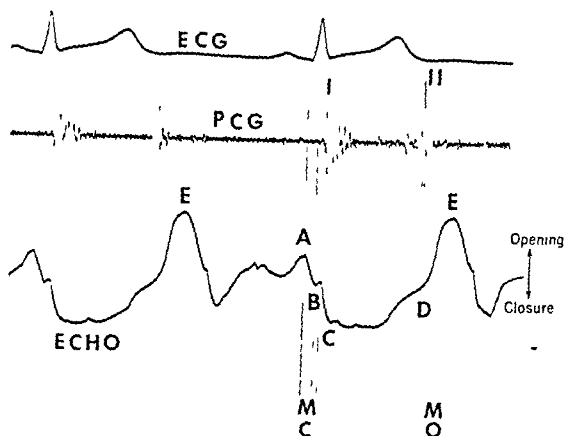


Fig 9 Echocardiogram of the anterior leaflet of the mitral valve (A mode—oscillographic tracing) in a 32 year old normal male Electrocardiogram and phonocardiogram with a contact microphone applied to the 3rd left i c s high pass filter with nominal frequency (100 Hz. and slope 24 db per octave) The B point of the echo slightly precedes the first high frequency component of the first heart sound MC = mitral closure MO = mitral opening

long series of vibrations that occur in early systole *the first sound*

2 In the case of the aorta the power resides in the aortic wall and the peripheral arterial walls, whose elastic and muscular structures have been placed under tension by the left ventricular contraction The vibrant mass includes the walls of the ascending aorta, the aortic valve the outflow tract of the left ventricle and the blood contained both in the ascending aorta and in the infundibulum The result is a short series of vibrations occuring in early diastole *the aortic component of the second sound*

3 A similar phenomenon occurs in the pulmonary artery causing *the pulmonary component of the second sound*

The lack of identifiable vibrations for the *right ventricle* may be attributed to the shape of this chamber and to the modality of its contraction (the outflow tract contracts normally later than the inflow tract so that 'damping of possible vibrations would occur) Moreover, as the contraction of the right ventricular inflow tract and that of the left ventricle are separated by a very short interval, separate groups of vibrations cannot be identified.

An article published during the preparation of this manuscript[59] claims to disprove some of the statements made by us Analysis of the technique and results of these authors however, shows that this is not the case because (1) suture of the flowmeter to the mitral annulus would cause *simulation of mitral flow* through rise of the probe caused by ventricular pressure rise and (2) absence of *a* waves in the left atrial pressure tracings, as well as a reduced filling period in mitral flow tracings suggest a severely compromised left atrial function

Were their tracings correct, mitral flow would have continued until left ventricular pressure was about 30 mm Hg higher than left atrial pressure, and the isovolumic period of the left ventricle would have been shortened by about 50 per cent

Summary

The mechanism of production of the first and second heart sounds is re examined on the basis of known physical laws and physiologic experiments of the last decade

A general theory is propounded which agrees with the observed facts and is in line with previous conclusions of both early and present physiologists

Three power sources are identified in the cardiovascular system valve closures occur before each sound while value tensions play only a secondary role

The accelerations and decelerations of the cardiovascular structures and of the blood they contain is the cause of all cardiac vibrations both inaudible and audible

This theory agrees with the conclusions of Luciani and of Wiggers and confirms the concept propounded by Rushmer

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Electrophysiology and pharmacology of cardiac arrhythmias II Relationship of normal and abnormal electrical activity of cardiac fibers to the genesis of arrhythmias

A Automaticity

Andrew L Wit Ph D*
Michael R Rosen M D*
Brian F Hoffman M D
New York N Y

Microelectrode techniques have enabled electrical activity of cardiac fibers to be studied under physiologic conditions as well as under the influence of a variety of external factors thought to simulate the conditions which cause arrhythmias in the in situ heart. More recently these methods have been used to study the electrical activity of cardiac fibers removed from diseased and arrhythmic hearts.[1-4] The results of these investigations have suggested interesting and plausible theories concerning the genesis of arrhythmias several such theories have been described in recent reviews[5-8] Here we will discuss some of the classical concepts of mechanisms responsible for arrhythmias and indicate how more recent investigations have suggested additional factors which may be responsible for disorders of the heart s rhythm

An arrhythmia is an abnormality in the rate regularity or site of origin of the cardiac impulse or a disturbance in conduction of the impulse such that the normal sequence of activation of atria and ventricles is altered. Arrhythmias thus may be said to result from abnormalities of impulse initiation impulse conduction or both[6] The electrical activity causing these abnormalities of impulse initiation and conduction may result from some change in the normal ionic mechanisms responsible for the generation of the transmembrane action potential of atrial ventricular or Purkinje fibers Abnormalities of impulse generation and conduction also may result from a different type of electrical activity with an ionic basis and electrophysiological characteristics quite unlike that which is normal for these fibers

I Two types of electrical activity in cardiac fibers fast and slow responses

Fast cardiac fibers and the fast response The fast fibers of the heart are those cardiac fibers which conduct electrical activity at a relatively rapid rate (0 5 to 5 M per second) This group includes working atrial and ventricular muscle fibers and fibers in the specialized conducting systems of the atria and ventricles This property of fast conduction and other related electrophysiologic characteristics which are described below are dependent on a transmembrane action potential with a rapid rate of depolarization This type of action potential has been called the fast response by Cranefield Wit and Hoffman[9] (Fig 1 A)

Under physiologic conditions the transmembrane potential of working atrial and ventricular

From the D partment of Pharmacology Coll ge of Physic ans and Surgeons, Col mbia University New York.

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Reprint requests Mi hael R Rosen, M D Dept. of Pharmacology College of Physicians a d Surgeons, Columbia Un v rsity New York N Y 10032.

D Wit and Dr Rosen are Senio In e tigators f the New York Heart Association. D R sen is Research Fellow of the John Polach k Foundation.

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mitral and tricuspid valve leaflets This property of slow conduction is dependent on a transmembrane action potential with a slow rate of depolarization This type of action potential has been called the slow response by Cranefield Wit and Hoffman[9]

The electrophysiologic characteristics of the sinus and A V nodes A V ring and mitral and tricuspid valve leaflets are entirely different from those described for the fast cardiac fibers[6 16] The slow fibers have a low resting membrane potential between −70 and −60 mV and on excitation a slow regenerative depolarization phase which carries the transmembrane potential to a value of only 0 to +15 mV (Fig 1 B) This slow depolarization phase is not dependent on sodium influx through a fast membrane channel[12 15] but rather due to a weak inward current possibly carried by calcium through a slow membrane channel[9 14 15] This channel is also inactivated slowly resulting in a prolonged phase of repolarization There is no evidence for fast sodium channels in these fibers. The depolarization phase is not affected by tetrodotoxin but is depressed by manganese or verapamil agents which block the slow membrane channel.[14 15]

The slow response is not recorded from these types of fibers only Disease processes may alter the ionic mechanisms underlying action potential generation in atrial ventricular or Purkinje fibers so that they also show slow response activity Therefore disease may convert fast fibers to slow fibers Many diseases which are associated with the occurrence of cardiac arrhythmias result in a reduction of the resting membrane potential of fast cardiac fibers[1 4 8] This in turn causes inactivation of the strong inward sodium current and the fast response at membrane potentials less than −60 mV, inactivation is complete[17] and a rapid sodium dependent depolarization no longer can be elicited However, the mechanism for the slow inward current is not inactivated at this level of membrane potential Consequently excitation may result in regenerative depolarization and an action potential which is due entirely to the activation of the slow inward current (Fig 1 B) The depolarization phase of this action potential is now insensitive to tetrodotoxin but can be blocked by manganese or verapamil[18 20]

The electrophysiologic properties of the slow fibers favor the occurrence of cardiac arrhythmias The low rate of depolarization (less than 10 V per second) and the low amplitude of the action potential result in extremely slow conduction The slow response also has a low safety factor for conduction and is prone to block at branch points in the cardiac syncytium where it encounters impediments to forward conduction[8] Unidirectional conduction block i e conduction in one direction along a bundle of cardiac fibers but not in the other direction is commonly associated with the slow response[8] During repolarization the electrophysiologic characteristics of slow fibers also differ from those of the fast fibers When action potentials are due to the slow response application of a depolarizing stimulus early during repolarization may sometimes evoke a new response but during the latter phase of repolarization the fiber is refractory[8 9] Refractoriness far outlasts full repolarization and normal conduction and excitability are not completely regained for many milliseconds after repolarization is complete (Fig 2 B)

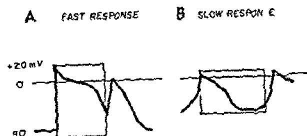


Fig 2 Recovery of excitability in fibers with fast and slow response action potentials Panel A shows a fast response action potential. The shaded area indicates the time after depolarization during which this cell is inexcitable When the cell has repolarized to approximately −55 mV, an action potential can be elicited by another stimulus Panel B shows a slow response action potential. The shaded area also indicates the time after depolarization during which this cell is inexcitable This time period outlasts complete repolarization so that a second action potential cannot be elicited until long after maximum diastolic potential has been reached

II Automaticity in fast and slow cardiac fibers The normal rhythm of the mammalian heart results from spontaneous excitation of cells in the sinus node In such cells immediately after the end of repolarization membrane potential slowly decreases this slow spontaneous depolarization during diastole (phase 4) lowers the membrane potential to threshold potential and a spontaneous action potential occurs. These fibers are therefore automatic In addition to the

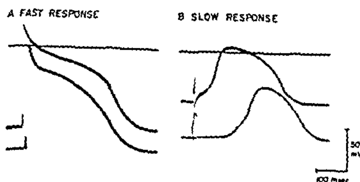


Fig 1 Comparison of the fast and slow response Panel *A* shows two transmembrane action potentials recorded from different cells in a bundle of canine Purkinje fibers (fast fibers) perfused with normal Tyrode's solution ([K+] = 4 mM) The reference 0 line is for the top action potential only The microelectrodes are located 15 mm apart at either end of an unbranched bundle and the Purkinje fiber bundle is being stimulated at one end. The action potentials shown in panel *A* are examples of the fast response They have high resting potentials (−90 mV) and the rates of depolarization are so rapid that the upstrokes are not visible Action potential amplitude is also large (125 mV) Conduction of the impulse between the two microelectrodes is very rapid the depolarization phases of both action potentials occur nearly simultaneously Panel *B* shows transmembrane action potentials recorded from the same two cells while the Purkinje fiber bundle is being perfused with Tyrode's solution containing a high [K+](16 mM) and epinephrine The high [K+] has depolarized the cells to resting membrane potentials of −60 mV, thereby inactivating the fast response Stimulation of the Purkinje fiber bundle now results in slow response action potentials Note that the upstrokes of both action potentials are very slow and the action potential amplitudes are low (< 80 mV) In addition conduction between the two microelectrodes is extremely slow it now takes the impulse 100 msec to propagate the distance of 15 mm between the two microelectrodes

muscle fibers and fibers of the specialized atrial and ventricular conducting system are characterized by a resting membrane potential between −80 and −95 mV and on excitation a rapid regenerative depolarization which is activated at a threshold potential of about −70 mV and which rapidly carries the transmembrane potential to a value of +25 to +35 mV This rapid depolarization is dependent on a large influx of sodium ions carrying a strong inward current through specific membrane channels These channels which control sodium conductance of the membrane respond rapidly to a change in transmembrane potential, resulting in the rapid depolarization or fast response [9] This phase of fast depolarization can be prevented by tetrodotoxin, a pharmacologic agent which specifically blocks the "fast" sodium channel.[10] Sodium conductance of the membrane is then inactivated rapidly, resulting in a rapid decline and cessation of the strong inward sodium current. In addition in these fast fibers a second inward (depolarizing) current is activated when the fast depolarization phase has lowered membrane potential to values less negative than about −55 mV This is a much weaker current than the initial sodium current and is probably carried by calcium through a "slow" membrane channel distinct from the fast sodium channel [11,12] This current is not affected by tetrodotoxin Since the "slow" membrane channels are activated slowly and the density of this current is low in comparison to the initial inward sodium current, it does not contribute significantly to the rapid depolarization phase of the normal action potential However, inactivation of this secondary inward current is slow, the current still flows after the initial rapid depolarization phase is over and maintains the membrane in a depolarized state It thus is primarily responsible for the plateau phase of the action potential [12]

Because of the nature of the voltage and time dependence of the mechanisms which control the "fast" sodium channels, fibers which generate action potentials by this fast response mechanism have certain characteristic electrophysiologic properties The large resting potential the value of the threshold potential (−70 mV), the rapid rate of depolarization (which may approach 1,000 V per second in Purkinje fibers) and the large amplitude of depolarization (100 to 130 mV) result in relatively rapid conduction in the fast fibers (Fig 1 *A*) Fast responses have a high safety factor for conduction so that propagation of the impulse usually is not blocked by minor electrical and anatomic impediments to its spread. Since sodium conductance is inactivated upon depolarization a stimulus applied during repolarization fails to elicit an active response until the membrane potential has returned to around −55 mV At this value only a subnormal regenerative response can be elicited (Fig 2, *A*) A normal response can be elicited only when repolarization has restored the normal resting potential and recovery of excitability accompanies repolarization

Slow cardiac fibers and the slow response The slow fibers of the heart are those cardiac fibers which conduct electrical activity at a relatively slow rate (0 01 0 1 M per second) This group includes the sinus and atrioventricular (A V) nodes, the cardiac fibers in the A V ring, and the

of spontaneous diastolic depolarization this possibly indicates the importance of an inward sodium current during phase 4[24] Increasing extracellular [Ca+] slows the automatic rate of these fibers by decreasing the threshold potential[5]

Automaticity in slow fibers. A second mechanism for spontaneous diastolic depolarization probably exists only in slow cardiac fibers This spontaneous diastolic depolarization occurs at low maximum diastolic potentials of *−60 mV or* less (Fig 3 *B*) At these membrane potentials the mechanism for automaticity associated with the fast response is probably inactivated as is the fast inward sodium current. *The ionic basis for spontaneous diastolic depolarization under these circumstances is uncertain*

The prototype for spontaneous diastolic depolarization in slow fibers is the sinus node This type of automaticity also occurs in cardiac fibers of the mitral and tricuspid valves[16,22] (Fig 3 *B*) and possibly in fibers of the lower A V node All these cells have low maximum diastolic potentials This type of automaticity can also occur in Purkinje fibers (which are normally fast fibers) if they are depolarized to low levels of membrane potential thereby inactivating both their normal mechanism for automaticity and the fast response or if they are exposed to a sodium free environment which has the same effect (Fig 3 *B*)[18,20]

Spontaneous diastolic depolarization in slow fibers may not be suppressed by elevating extracellular [K+] In fact the automatic rate of fibers in the sinus node[23] and mitral valve leaflets actually increases with moderate *increases in* extracellular [K] (up to 12 mM) Automaticity of this type is also little affected by lowering extracellular [Na] to 50 per cent of normal and may be enhanced by moderate elevations in extracellular [Ca][19,25] This may indicate the presence of an inward calcium current during diastole

III Factors which may shift the site of impulse origin The site of impulse origin or pacemaker of the heart usually is the region which initiates impulses at the fastest rate Normally the sinus node possesses the greatest *degree of* automaticity Impulses arising here conduct throughout the myocardium and prevent latent pacemaker cells in other regions of the heart from spontaneously *depolarizing to threshold* potential[26] If the automaticity of the sinus node is suppressed or if conduction of the impulse arising in the sinus node is impaired, spontaneous diastolic depolarization of cardiac fibers in *the specialized* atrial or ventricular conducting systems A V valves or A V junction *may reach threshold* potential and impulses may be initiated in these regions Marked vagal *activation will inhibit sinus node* automaticity as well as automaticity of other atrial pacemakers Since the effects of the vagus nerve on automaticity of Purkinje fibers in the *ventricle are minimal* spontaneous diastolic depolarization may still occur in these fibers and *reduce their* membrane potential to threshold resulting in impulse initiation in the ventricular conducting system Similar events may occur in either the atrial or ventricular conducting system in the presence of sinoatrial conduction block or in the ventricular conducting system in the presence of atrioventricular block Under these circumstances either of the mechanisms for spontaneous diastolic depolarization described above may be responsible for the automatic impulse initiation If the impulses arise in atrial specialized fibers or Purkinje fibers with maximum diastolic potentials greater than −60 mV automaticity is of the type which is associated with fast response activity If the impulses arise in slow fibers of the A V valve leaflets or A V junctional region then automaticity is of the type associated only with slow cardiac fibers and the slow response

In instances where sinus node function is normal or depressed, enhancement of spontaneous *diastolic depolarization of latent* pacemaker cells by environmental alterations or disease processes *may result in a shift in the site of the* pacemaker If spontaneous diastolic depolarization is enhanced to the degree that it carries membrane potential of latent pacemaker cells to threshold potential before the cells are passively depolarized by propagating electrical activity an impulse will be initiated in the ectopic site and will activate part or all of the heart resulting in single ectopic atrial or ventricular impulses or sustained atrial or ventricular rhythms

Enhanced automaticity which results in arrhythmias may also occur in fibers with either of the two mechanisms for spontaneous diastolic depolarization One example is the enhanced automaticity of latent pacemakers which *results* from *sympathetic activation* The resultant release of catecholamines increases the rate at

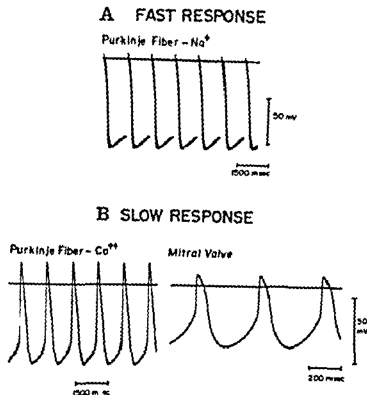


Fig 3 Spontaneous diastolic depolarization and automatic impulse initiation in cardiac fibers with fast and slow response activity Panel *A* shows action potentials recorded from a canine Purkinje fiber with a maximum diastolic potential of −90 mV and therefore fast response activity This fiber has prominent spontaneous diastolic depolarization and is not being electrically stimulated. Panel *B*, left, shows slow response calcium dependent action potentials recorded from a canine Purkinje fiber perfused with a sodium free medium Maximum diastolic potential is −65 mV spontaneous diastolic depolarization is prominent, and the fiber is automatically active Panel *B*, right, shows slow response action potentials recorded from a cardiac fiber in the mitral valve leaflet of a monkey Maximum diastolic potential is −58 mV Note the prominent phase 4 depolarization and automatic activity The fiber is not being electrically stimulated

fibers of the sinus node a number of other types of cardiac fibers possess the property of automaticity These include specialized atrial fibers [6,21] fibers in and around the coronary sinus ostium [5] cardiac fibers in the tricuspid and mitral valve leaflets [16,22] and fibers in the distal part of the A V node and His Purkinje system [5] Under certain conditions these fibers may also spontaneously initiate action potentials

There is probably more than one ionic mechanism for spontaneous diastolic depolarization and the resultant automaticity This is suggested by observations that (1) alterations in ionic environment affect spontaneous diastolic depolarization of some automatic fibers in one way and spontaneous diastolic depolarization of other automatic fibers in a different way For example elevation of extracellular [K+] suppresses automaticity of Purkinje fibers but not mitral valve fibers, (2) antiarrhythmic drugs may depress or abolish spontaneous diastolic depolarization of some fibers but not others, and (3) fibers with spontaneous diastolic depolarization and automaticity may respond in different ways to electrical stimulation Different mechanisms for automaticity are of obvious clinical significance since they can explain the failure of some seemingly automatic rhythms to be affected in a predictable manner by drug or electrical therapy

Automaticity in fast fibers The fast fibers in the atrial and ventricular specialized conducting systems are capable of spontaneous diastolic depolarization and automatic impulse initiation (Fig 3 *A*) Spontaneous diastolic depolarization begins immediately after repolarization at a maximum diastolic potential significantly greater than −60 mV and results from a time and voltage dependent decrease in membrane potassium conductance and a co existing steady inward sodium current. When the rate of spontaneous diastolic depolarization is rapid and threshold potential is normal the resultant action potential will have a fast sodium dependent depolarization phase or fast response (Fig 3 *A*) Under certain conditions part of the fast fiber action potential i e the upstroke and repolarization phases can be converted to the slow response while the mechanism for spontaneous diastolic depolarization remains characteristic for fast fibers. This occurs if maximum diastolic potential remains high but the rate of spontaneous diastolic depolarization is slow and threshold potential is shifted towards 0 Now the fast sodium current will be inactivated during the slow phase 4 depolarization and only the slow inward calcium current will be activated when membrane potential has reached threshold A slow response action potential will result

Since the spontaneous diastolic depolarization that occurs in fast fibers is the result of a time and voltage dependent decrease in membrane potassium conductance its slope is enhanced at an extracellular [K+] less than 3 mM (because decreasing extracellular [K+] decreases potassium conductance) and it is suppressed at an extracellular [K+] greater than 3 m M (since elevation of extracellular [K+] increases potassium conductance) Decreasing extracellular [Na+] also depresses the automatic rate of fibers with this type

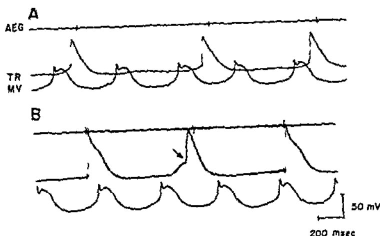


Fig 5 The preparation consists of the anterior atrial wall and attached mitral valve leaflet of the dog The top trace in each panel is the electrogram recorded from the atrial wall (AEG) the middle trace shows action potentials recorded from the transitional region (TR) between atrium and valve and the bottom trace is recorded from a spontaneously depolarizing mitral valve fiber (MV) In panel *A* the mitral leaflet was spontaneously active at a cycle length of 450 msec and there was 3 1 conduction block between the valve leaflet and left atrial wall In panel *B* during the spontaneous activity in the valve leaflet the atrial wall was stimulated at a cycle length of 1 600 msec Thus stimulated atrial activity depolarized the fiber in the transitional region (not the same fiber as in panel *A*) but was not conducted into the mitral valve leaflet Occasional impulses however were conducted from the valve leaflet to the atrium (arrow) simulating parasystolic beats. Note the slow prepotential and reduced amplitude of the action potential in the transitional region when the impulse arising in the valve conducted to the atrium (arrow) (*Reproduced from* Circ Res [15] by permission of the American Heart Association.)

having extremely low upstroke velocities and amplitudes (Fig 4) The mechanism for this spontaneous depolarization is probably that which is associated with slow cardiac fibers

Parasystole It is quite likely also that parasystolic impulses or rhythms arise as a result of spontaneous diastolic depolarization of fibers with low membrane potentials and slow response activity Parasystole results if an automatic focus is protected from the basic rhythm by entrance block the (sinus) impulse thus is prevented from exciting the parasystolic focus Variable exit block may sometimes confine the parasystolic impulses to the parasystolic focus [28] The existence of a focus guarded by both entrance and exit block can be seen on the electrocardiogram only if intermittent relief of exit block allows the focus to excite the atria or ventricles.

The conditions of entrance or exit block are more easily satisfied in areas with properties of the slow response since conduction in such areas is more prone to block than in areas with properties of the fast response For example in the normal heart the mitral valve leaflets form a natural site for an atrial parasystolic focus (Fig 5) Cardiac fibers in the transitional region between the atrium and the cardiac muscle in the valve leaflet have low resting potentials slow rates of depolarization and resulting slow conduction and are prone to develop conduction block which may be unidirectional Conduction of atrial impulses may readily be blocked in this region without depolarizing cardiac muscle fibers in the valve leaflet [15] These valvular muscle fibers may be spontaneously active and the impulses originating in them may penetrate into the transitional region keeping it refractory to incoming impulses of sinus origin If the sinus cycle is sufficiently long occasional impulses arising in the mitral valve will be able to conduct through the transitional area into the atrium and cause parasystolic atrial impulses (Fig 5)

Parasystole also may occur in other regions of the heart with slow response activity It is more frequently encountered in chronically diseased hearts or in association with myocardial infarction [28] The parasystolic focus itself or the conditions of entrance and exit block may be inferred to result from a severe reduction in membrane potential of cardiac tissue caused by disease and

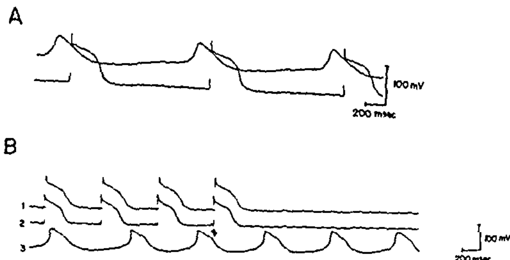


Fig 4 Spontaneously occurring action potentials in the subendocardial Purkinje network surviving in a region of *extensive myocardial infarction. In Panel A* the top trace is recorded from a subendocardial Purkinje fiber in the infarcted region This fiber shows a low maximum diastolic potential (about −55 mV) spontaneous diastolic *depolarization* and a slow action potential upstroke It thus shows slow responses and appears to be automatically active (the preparation is not being electrically stimulated) The bottom trace shows an action potential recorded from a subendocardial Purkinje fiber in an adjacent noninfarcted region Note the large resting membrane potential (−90 mV) and fast upstroke (fast response) This fiber does not show spontaneous diastolic depolarization The fiber in the infarction with slow response activity appears to be the pacemaker for the preparation this fiber depolarizes 200 msec before the fiber in the adjacent normal region Panel *B* shows action potentials from another infarcted preparation The top two traces are recordings of transmembrane potentials with high maximum diastolic potentials and fast upstroke velocities (fast responses) The action potentials are activated by an electrical stimulus The bottom trace shows potentials recorded from a subendocardial Purkinje fiber surviving in the infarcted region Its maximum diastolic potential is low there is prominent phase 4 depolarization and the upstroke is slow Furthermore it is spontaneously active Electrical activity initiated by the stimulus is not propagating into this region The action potentials on the bottom trace are not temporally related to the action potentials in traces 1 and 2 and, therefore there is entrance block At the arrow electrical stimulation is terminated but spontaneous activity in trace 3 continues. These impulses do not activate other regions of the preparation Therefore there is also exit block from this site

which spontaneous diastolic depolarization carries membrane potential to threshold in normal atrial specialized fibers, fibers of the A V valves or Purkinje fibers Catecholamines, therefore, enhance spontaneous diastolic depolarization of both fast and slow fibers and thereby may initiate atrial or ventricular tachycardias

Automaticity resulting from cardiac disease Disease processes may also result in the development of spontaneous diastolic depolarization and automatic impulse initiation in cardiac fibers This automaticity most likely will be the type associated only with slow fibers if there is a significant reduction in the membrane potential of the affected cells [2,4] Many cells in atrial muscle excised from patients with diseased atria or atrial arrhythmias show a low resting potential (< −60 mV) and low amplitude action potentials with low rates of depolarization These cells also may show spontaneous diastolic depolarization and automatic activity [1] Within an hour after coronary artery occlusion cells with similar low amplitude action potentials and spontaneous diastolic depolarization have been demonstrated in ventricular intramural regions of acute myocardial infarction [27] These cells may be ventricular muscle fibers altered by the effects of ischemia Most muscle cells within the depths of the infarction die within several hours after coronary occlusion and no longer generate action potentials (Fenoglio Allen and Wit unpublished observation) However the subendocardial Purkinje fibers underlying regions of extensive myocardial infarction usually survive but have abnormal electrical activity In such subendocardial Purkinje fibers spontaneous diastolic depolarization may be marked and may initiate ectopic, automatic impulses for several days after coronary occlusion [24] In these Purkinje fibers spontaneous diastolic depolarization occurs in association with low maximum diastolic potentials (−60 mV or less) and with action potentials

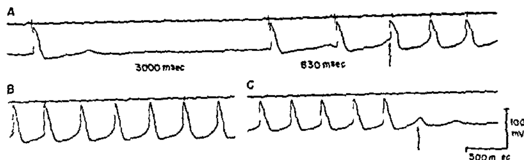


Fig 6 Induction of spontaneous activity by electrical stimulation of fibers showing slow response action potentials in the mitral valve leaflet of the monkey The top trace in each panel shows an atrial electrogram and the lower trace is an action potential recorded from a mitral valve fiber In panel *A* the atrium was stimulated at cycle length of 3 000 msec and activity propagates into and activates the cell in the mitral valve leaflet (first two action potentials) Note the hyperpolarization and subsequent subthreshold depolarization following repolarization of the mitral valve fiber After the first two action potentials, the stimulus cycle length was abruptly decreased to 830 msec resulting in an action potential soon after the subthreshold after depolarization of the previous response The hyperpolarization following the action potential elicited at a cycle length of 830 msec is succeeded by a *supra* threshold depolarization leading to a spontaneously occurring action potential which propagates to the atrium (arrow)—the electrical stimulus has been turned off This is followed by repetitive spontaneous activity in the mitral valve leaflet which is also shown in panels *B* and *C* In panel *B*, only some impulses propagate to the atrium Finally in panel C, spontaneous activity of the valve fibers ceases when the after depolarization fails to reach threshold (arrow)

antiarrhythmic drugs may be effective against arrhythmias resulting from one type of automaticity and not the other An example of this differential effect is provided by comparing the actions of antiarrhythmic agents on the spontaneous diastolic depolarization which occurs in Purkinje fibers with maximum diastolic potentials significantly greater than −60 mV (and, therefore may be associated with either fast or slow response activity) and on the spontaneous diastolic depolarization which is always associated with slow response activity as in the sinus node Agents such as diphenylhydantoin and lidocaine can suppress spontaneous diastolic depolarization in such Purkinje fibers at concentrations which have little or no effect on impulse initiation in the sinus node the mechanism underlying spontaneous diastolic depolarization in sinus node fibers thus is not affected by these concentrations of the drugs [36,37] Automatic activity of other fibers which have the mechanism for spontaneous diastolic depolarization associated only with the slow response may also be resistant to antiarrhythmic drug effects Although the evidence is still limited, impulse initiation in mitral valve fibers also may be resistant to the actions of the commonly used antiarrhythmic drugs Automaticity in diseased atrial muscle with low membrane potentials is not suppressed by procaine amide in a concentration ten times greater than that which abolishes automaticity of Purkinje fibers with fast response activity [38] In Purkinje fibers perfused with a solution lacking sodium the automaticity is of the type always associated with slow response activity and is not abolished by high concentrations of quinidine (Wit Wiggins and Cranefield unpublished observations) Automaticity of some subendocardial Purkinje fibers with maximum diastolic potentials less than −60 mV surviving in areas of extensive myocardial infarction is insensitive to the anti automatic effects of lidocaine (Allen and Wit unpublished observation) Perhaps these observations will explain why some arrhythmias of automatic origin are resistant to antiarrhythmic drug therapy

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the resultant slow response activity The degree of depression (depolarization of the cell membrane and associated electrophysiologic changes) may vary markedly between regions separated by only a few millimeters A small area may show a resting potential of −55 mV and display spontaneous activity while an adjacent area which is only slightly more depolarized may show various degrees of conduction block resulting in either entrance or exit block Such areas have been directly demonstrated in chronically diseased atrial muscle [29] They also occur in the subendocardial Purkinje fiber network surviving in regions of extensive myocardial infarction within 24 to 48 hours after the coronary artery occlusion (Fig 4) [24]

IV Effects of electrical stimulation on automatic impulse initiation Electrical stimulation of the heart is often used to control or abolish certain clinical arrhythmias and recently has been utilized in an attempt to determine whether an impulse is due to automatic impulse initiation or to re entry [30] However in light of more recent knowledge concerning the two types of automaticity such a distinction may be more difficult than previously supposed The physiologic pacemakers of the heart, which include the slow fibers of the sinus node (spontaneously depolarizing by one type of automatic mechanism) and the fast fibers of the atrial and ventricular conducting system (when they are spontaneously depolarizing by their normal automatic mechanism) respond to electrical stimulation in the manner predicted for automatic foci When automatic fibers showing fast response activity are stimulated electrically at a rate more rapid than their spontaneous rate a phenomenon known as overdrive suppression occurs [31] The electrical stimulation causes hyperpolarization and depression of the slope of spontaneous diastolic depolarization As a result when electrical stimulation is terminated there is a period of quiescence, the duration of which is related to the frequency of stimulation This is followed by the eventual reappearance of spontaneous activity first at a slow rate and then at a gradually faster one until the original rate is attained Electrical stimulation of the heart during an ectopic rhythm may result in a similar behavior electrical stimulation will activate the heart and overdrive the ectopic focus if the rate of stimulation is rapid enough unless there is entrance block into the focus When the stimulus is turned off there will be a short period of quiescence with a gradual resumption of the ectopic rhythm This response to electrical stimulation has been interpreted as indicating the presence of an automatic focus

Electrical stimulation has a different effect on the slow fibers of the mitral valve (Wit unpublished observations) and on Purkinje fibers when their normal fast response activity and associated automaticity have been converted to characteristic slow fiber activity [32] In these fibers, electrical stimulation may enhance spontaneous diastolic depolarization and automaticity and therefore cessation of electrical stimulation may be followed by tachycardia rather than by overdrive suppression A similar effect has also been observed in Purkinje fibers poisoned by digitalis [33-35] In mitral valve fibers the action potential generated in response to an electrical stimulus is often followed by an after hyperpolarization which either decays to the level of resting potential or may continue beyond the previous resting potential to produce a subthreshold depolarization (Fig 6) If the rate of stimulation is increased this subthreshold depolarization may increase in amplitude until it carries membrane potential to threshold. When this occurs a spontaneous action potential results coupled to the previous driven response In turn the oscillatory after depolarization of this spontaneous action potential may also reach threshold giving rise to a second spontaneous action potential This process may continue resulting in a train' of spontaneously occurring action potentials (Fig 6) Such a run of spontaneous action potentials ceases when the after depolarization fails to reach threshold.

A single premature electrical stimulus may have a similar effect Therefore a premature stimulus may induce sustained automatic activity in these fibers Here, induction of tachycardia by a premature stimulus does not necessarily prove that it is due to re entry as has previously been supposed [30] A premature stimulus will not induce automaticity in fibers with the mechanism for automaticity associated with the fast response unless some pharmacologic intervention has been imposed

V Significance of two types of automaticity It is obvious that if there is more than a single mechanism for spontaneous diastolic depolarization and automatic impulse initiation certain

Annotations

Coronary arteriography Reduced patient risk using a new technique

With the recent advent of direct myocardial revascularization using a saphenous vein aortocoronary artery bypass graft coronary arteriography has become a widely used diagnostic tool When deciding on the desirability of performing coronary arteriography on any given patient the useful information to be gained must be balanced against the inherent hazards of the procedure When performed by the Sones technique the primary complication of art ry catheterization is brachial vascular occlusion with thrombus formation The incidence of morbidity has been reported to be as high as 24 per cent,[1 2] sometimes resulting in impaired circulation distal to the arteriotomy The Judkins technique of performing coronary arteriography via a percutaneous femoral artery catheterization also carries some specific potential complications These include the possibility of injection of a fibrin clot into one of the coronary arteries with a mortality rate as high as 2 4 per cent[3 4] It has been postulated that fibrin clots formed on the intravascular guide wire used during this procedure may be stripped off during the change of catheters The possibility of this complication is therefore enhanced by the multiple catheters required for Judkins technique Occasionally fibrin emboli will cause central nervous disturbances and, more frequently impaired peripheral arterial circulation.[5-10] There is also a greater risk of occlusion of the coronary ostia using the percutaneous femoral catheters because of the absence of side holes When the aortic valve is stenotic it may be difficult to advance the preformed percutaneous femoral artery catheter into the left ventricle

To minimize the inherent risk of the procedure a combination of the two techniques was recently employed. After percutaneous femoral artery puncture with a standard arterial needle a 0 038 inch teflon coated guide wire was advanced into the femoral artery The needle was then removed. The entire study was then carried out, using only the 8F Sones catheter

We used a 100 cm. Sones catheter which was satisfactory for left ventriculography and for coronary arteriography It must be emphasized that the same number of wire from different manufacturers may not fit the same catheter Thus a Cordis 0 038 inch teflon coated guide wire did not allow for satisfactory introduction of the 8F Sones catheter over the wire whereas a presumably similar 0 038 inch teflon coated guide wire supplied by Universal Medical Instrument Corporation allowed passage of the catheter with ease Therefore the wire should be fitted into the catheter prior to each procedure

Cut films can also be obtained with Sones catheter as shown in Fig 3

Although we have not yet performed coronary angiography using this combined technique on enough patients to be able to offer statistical evidence confirming a lower incidence



Fig 1 The tapered tip of the Sones catheter can be seen traversing the aortic valve. In the lower left corner the more proximal part of the catheter can be seen in the descending aorta.



Fig 2 An aortogram demonstrates the eccentric deformed aortic orifice of the patient in Fig 1 A pigtail catheter could not be passed across this valve with or without a guide wire

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Table I Adrenergic activity in smokers and nonsmokers with acute myocardial infarction

	Smokers (n = 8)		Nonsmokers
Twenty four hour catecholamine excretion	145 ± 10 μg/24 hour	p < 0 005†	88 ± 7μg/24 hour
QS_2I	502 ± 3	p < 0 005	515 ± 2

ISEM
†Student s t te t.

Table II Serious early arrhythmias in acute myocardial infarction

	Smokers	Nonsmokers
Supraventricular tachycardia	1	1
Frequent multifocal premature ventricular contractions	3	1
Ventricular tachycardia	2	1
Ventricular fibrillation	1	0
No serious arrhythmia	1	9
Total incidence of serious arrhythmia	7/8 = 87%	3/12 = 25%
	p < 0 02*	

Fisher s exact test.

acidosis hypotension, and drugs which could contribute to the production of arrhythmias Twenty four hour urinary collections for catecholamine excretion and systolic time intervals were obtained within the first twenty four to forty eight hours of hospitalization in all patients The technique for measuring catecholamines and systolic time intervals in our laboratory has been previously described.[20 2] The normal range for electromechanical systole corrected for heart rate (QS_2I) is 546 ± 14 msec (1 S D) and for urinary catecholamine excretion in hospitalized normal subjects it is 48 ± 16 μg per 24 hours (1 S D) Arrhythmias were detected by standard coronary care unit constant monitoring procedures backed up by an automatic sequencing device which produced 10 second rhythm strips four times per hour

Eight of the twenty patients were chronic heavy cigarette smokers up to the time of admission (twenty or more cigarettes per day) and twelve were nonsmokers. Smoking was not allowed after admission. These two groups did not differ statistically in age size of infarction judged from serum SGOT and LDH values or in severity of left ventricular dysfunction judged by clinical examination and the ratio of the PEP/LVET[23 26] There were no deaths during hospitalization in either group.

Smokers had a significantly higher incidence of serious arrhythmias, higher urinary catecholamine excretion, and a shorter value for total electromechanical systole (Table I and II) Only two patients (nonsmokers) had normal catecholamine excretion. The increased catecholamine excretion was probably not secondary to arrhythmia since all but two patients developed the arrhythmia after the collection.

The explanation for these relationships is not entirely clear from our data. It is unlikely that the direct effect of nicotine played a role in the genesis of the arrhythmias since smoking was discontinued after admission There was a higher level of adrenergic activity in the smokers which was associated with an increased incidence of significant arrhythmias. Whether these patients had higher adrenergic activity related to chronic stimulation by nicotine or whether these patients were chronically hyperadrenergic independent of cigarette consumption is not known.

It is recognized that the present series is small and does not include the complete spectrum of acute myocardial infarction However two groups were comparable with respect to the clinical severity of the infarct and were free of secondary factors which may have contributed to the arrhythmias Fisher s exact test which was employed to test the statistical significance of the different incidence of arrhythmia between the two groups is not influenced by sample size Therefore we believe that the relationship between smoking excessive catecholamine excretion and serious arrhythmia in acute myocardial infarction is real and merits further investigation It is also possible that a similar mechanism may play an important role in the higher incidence of sudden death in smokers with chronic coronary artery disease

Richard P Lewis M D
Harisios Boudoulas M D
Department of Medicine
The Ohio State University College of Medicine
410 West 10th Ave
Columbus Ohio 43210

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Fig 3 Cut film of left coronary angiography A significant proximal obstruction is seen in the large circumflex artery The left anterior descending artery is diseased throughout

of complications the foregoing procedure offers some of the advantages of each technique while reducing some of the risk factors

Branko Placik M D
Paul H Miller M D
Department of Cardiology
City of Hope Medical Center
Duarte Calif 91010

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Catecholamines, cigarette smoking, arrhythmias, and acute myocardial infarction

It is well known that coronary artery disease and sudden death are more common in cigarette smokers than in non smokers[1-5] It is also known that catecholamine excretion is increased in acute myocardial infarction[6-14] There is evi dence that patients with higher levels of catecholamine ex cretion have an increased incidence of arrhythmias Although nicotine has direct arrhythmic effects it is also an adrenergic stimulant[15-19] This latter effect may be of con siderable clinical significance in patients with ischemic heart disease

A recent study from this laboratory demonstrated a good correlation between the magnitude of increased catechol amine excretion and the shortening of electromechanical systole derived from systolic time intervals in patients with acute myocardial infarction[14] From this series twenty pa tients were obtained who met the following selection criteria they had a transmural infarction none had pulmonary edema or shock all had normal renal function and none were receiving drugs This selection was deliberate in order to minimize the influence of variables such as hypoxia

This study was supported in part by grants from the National Heart and Lung Institute National Institutes of Health (Program Project Award NIH 1 PO1 HE 11504 and Research Grant 1 RO1 HE 12660)

ml of isopaque coronar was given into the right coronary artery One minute later the patient complained of severe substernal pain. The ECG showed ST segment elevations in Lead I and ST segment depression in Leads II and III This was rapidly followed by a drop in blood pressure to zero Closed and open cardiac massage did not result in any response in the vital signs The patient was pronounced dead 60 minutes later

At autopsy thrombi were found in both right and left coronary arteries (Fig 1) The right coronary artery which was dominant was completely occluded in its posterior segment by a thrombus with a total length of 30 mm At the crux cordis this thrombus was wedged into the bifurcation of the main artery into the posterior descending branch and the continuation of the main artery over the posterior aspect of the left ventricle A small thrombus of approximately 1 mm. in length was found in the right coronary artery close to its ostium wedged into the ostium of a tiny conal branch The proximal segment of the left coronary artery was occluded by a saddle thrombus at the site of the bifurcation into the anterior descending and circumflex branches. More distally in the circumflex branch an obstructive thrombus was found with a total length of 15 mm. Microscopically each of these thrombi consisted of tightly coiled platelet fibrin aggregates (Fig 2) At the crux cordis, immediately proximal to the bifurcation a fragment of fibroelastic tissue was found embedded inside the thrombus (Fig 3 left) This closely resembled the fibroelastic inner layer of a coronary artery (Fig 3 right) Serial sectioning of the proximal part of the right coronary artery together with its ostium and the surrounding aortic wall revealed a minuscule laceration of the inner layer at the site of the ostium. Coronary atherosclerosis was of minor significance In its severest form, at the site of the bifurcation of the main left coronary artery there was less than 50 per cent narrowing of the lumen.

The occlusive thrombi in this case closely resemble those described by Preston Price and associates[3] and are considered by them to be thromboemboli transferred from the catheter Like in their patients the composition of fibrin platelet aggregates indicates a recent formation of these thrombi In our patient intimal laceration of the proximal part of the right coronary artery was found with parts of the fibroelastic layer present in the thrombus It is unlikely however that an embolus of 30 mm in length could have originated as a thrombus at the site of laceration in the right coronary artery The presence of thromboemboli in the left coronary artery seems to completely exclude the intimal laceration as a cause for the findings in our patient The occurrence of this complication seemed to be temporally related to the introduction of the Judkins catheter Since the time interval between the introduction of the catheter and initial complaints was only three minutes and since the catheter was carefully flushed in this interval an intraluminal origin of the thromboembolus is not likely Possibly the thromboembolic material originated from the external surface of the first catheter used, was stripped off at the arterial puncture site when this catheter was removed, accumulated at the guide wire and re introduced into the ascending aorta on the tip of the Judkins catheter

This mechanism, suggested by Takaro and co-workers[2] might also explain the fact that thromboembolic material was found in both coronary arteries, while only one coronary artery was entered This patient the only case of fatal thromboembolism in 250 consecutive arteriograms using this technique illustrates that careful flushing and fast handling of the catheter may not give full protection against thromboembolic incidents We wonder whether this complication is not occurring more frequently than suspected and might be responsible for myocardial infarction following coronary arteriography Like in the other cases reported coronary angiography in our patient was performed by the Judkins technique[4] As suggested by Giddings See and Lewis[1] Chahine Herman, and Gorlin,[6] and Preston Price and coworkers[3] the Judkins technique which comprises the use of guide wires, may have a higher incidence of thromboembolic complications than the transbrachial technique advocated by Sones[5] This may be partially explained by the routine administration of heparin in many laboratories applying the Sones procedure[7] Possibly systemic heparinization may also reduce the incidence of this complication in the Judkins

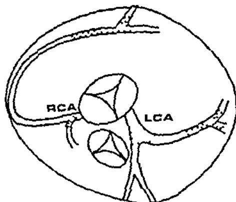


Fig 1 Schematic presentation of the localization of coronary thromboemboli Proximal in the right coronary artery a small embolus was found wedged in the ostium of a tiny conal branch.



Fig 2. Tightly coiled thromboembolus composed of platelet fibrin aggregates in the right coronary artery Elastic tissue stain, ×45

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Fatal thromboembolism during coronary arteriography

Thromboembolic complications following coronary arteriography are considered to be rare as compared to mechanical complications like inadvertent blocking of the artery and traumatic laceration of the arterial wall Recently however cases of fatal coronary thromboembolism have been documented [1-3]

Obstruction of a major coronary artery was caused in these patients by a tightly coiled thromboembolus composed of a delicate fibrin meshwork and aggregated platelets. It has been suggested that these emboli are derived from the luminal and external surfaces of the catheter or from its guide wire and not from primary thrombosis following laceration of the coronary artery [3] In this annotation a case is documented which may support this view

The patient was a 43 year old female who had a history of frequent attacks of dizziness and syncope starting five years prior to admission There was no history of infectious diseases No complaints suggesting coronary artery disease and no family history of sudden death or heart disease were present Neurologic examination and electroencephalogram (EEG) were normal No abnormalities were found on physical examination Her electrocardiogram (ECG) revealed frequent ventricular premature beats increasing on exercise with occasionally three ventricular premature beats in a row Left bundle branch block developed at heart rates above 130 per minute Right and left sided heart catheterization showed normal hemodynamics. To investigate whether coronary artery disease was responsible for her disabling arrhythmia which could not be satisfactorily controlled by drug therapy it was decided to perform coronary arteriography

A left ventricular cineangiogram revealed no abnormalities apart from a slightly decreased ejection fraction (0 52) Thirteen minutes after the cineangiogram was made the Teflon cineangiocatheter which was introduced in the right femoral artery using the Seldinger technique was exchanged for a Judkins catheter (Cordis) This catheter was carefully flushed with heparinized saline and advanced into the right coronary ostium Two minutes after the introduction of this catheter in the femoral artery a test injection of 2

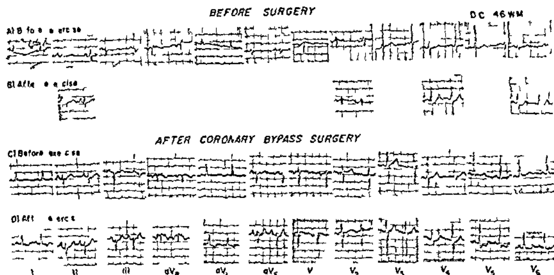


Fig 1 ECG of Patient D C before and after operation

agement Because of "intractable" angina pectoris he had coronary angiography and triple venous aorta coronary bypass surgery His pain was relieved, but he continued to have dyspnea on exertion and was impressed by the fact that he felt no better if not worse He sought other medical advice 16 months later and was found to have even more angina pectoris but it was silent " i e without the characteristic pain, the patient experiencing only dyspnea. A Master two step test showed greater ST segment and T wave changes associated with marked dyspnea during the test and an inability to walk the entire number of prescribed steps for the test (Fig 1) An echocardiogram showed a hypokinetic to akinetic septum while the patient was at rest and free from dyspnea He is now receiving medical treatment for active silent angina pectoris.

This patient is described briefly to emphasize the fact that absence of anginal pain or chest discomfort does not indicate the absence of angina pectoris This patient also emphasizes the importance of careful and thoughtful history taking and the need to realize that many patients with ischemic heart disease have silent angina manifested by dyspnea upon stress which is relieved quickly with rest and also with sublingual nitroglycerin.

George E. Burch, M D
Department of Medicine
Tulane University School of Medicine
New Orleans La. 70112

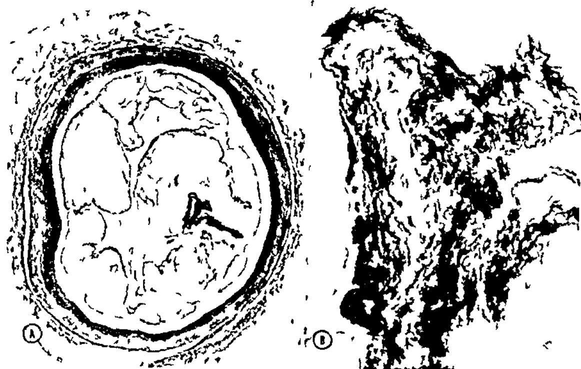


Fig 3 Right coronary artery at the level of the bifurcation at the crux cordis Embedded within the thromboem bolus is a loose embolized fragment of arterial wall Elastic tissue ×50 Right detail of the embolized fragment which is identified as the fibroelastic inner layer of the proximal segment of the right coronary artery Elastic tissue stain ×500

technique The ever increasing number of coronary angio grams made all over the world however requires a system atic investigation as to what technique should be used and what other measures should be taken to avoid this dreadful *complication*

A E Becker MD
H J J Wellens MD
R M Schuilenburg MD
D Durrer MD
Laboratory for Pathological Anatomy and
Department of Cardiology and Clinical Physiology
Wilhelmina Gasthuis
Amsterdam The Netherlands

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Silent angina and coronary bypass surgery

The relief of chest pain or *discomfort* characteristic of angina pectoris by coronary bypass surgery does not necessarily im ply a cure or relief of the angina pectoris or even improve ment of the myocardial circulation This is well illustrated by the patient described here who had silent angina pectoris after coronary bypass surgery

D C a 46 year old man had typical angina pectoris which became progressively worse with inadequate medical man

(87 531 532) requires additional comment Dr Benaim correctly emphasizes the clinical importance of transient arrhythmias and the benefit to the patient when a specific diagnosis can lead to specific treatment While it is helpful indeed if symptoms or "attacks" can be reproduced by the patient in the doctor s office or the patient is taught to continuously and accurately monitor his pulse rate and rhythm the inescapable evidence remains that the vast majority of patients escape detection unless a technique such as Holter monitoring is employed

Our experience with over 30 000 Holter tapes has revealed that the vast majority of clinically significant arrhythmias and conduction abnormalities are asymptomatic even in patients referred with a high index of suspicion. It is also usual that patients with symptoms will have many similar episodes recorded that are not accompanied by subjective symptoms. The patient with Stokes Adams syncope usually cannot feel his pulse during the event and elderly senile or anxious patients either cannot or should not be counting their pulse In addition the physician may be deprived of valuable or even critical information if the Holter technique is not employed. Ventricular extrasystoles may be close-coupled multifocal paired, or in short salvos of ventricular tachycardia. ST segment changes suggestive of ischemia may occur Rate dependent conduction abnormalities may occur Arrhythmias or conduction abnormalities may occur during sleep

In view of the simplicity of the Holter technique particularly with smaller and more reliable cassette recorders that are now becoming available we feel it would be incorrect to expose patients to the hazards and complications of drug toxicity or cardiac pacing without documentation of the suspected abnormality

Daniel J Bleifer MD
Selvyn B. Bleifer MD
Harold L Karpman, MD
Cardiovascular Medical Group of Southern California, Inc
Beverly Hills, Calif 90210

Reply

To the Editor

The Holter monitoring technique is certainly a useful diagnostic aid in the evaluation of patients suspected of suffering from intermittent cardiac dysrhythmias Unfortunately it is not the complete answer to the problem as it has definite drawbacks

The arrhythmic episodes may be so infrequent that the time will be reached when the patient and/or the doctor will give up hope of obtaining the answer and abandon the monitoring before an episode occurs Some patients are reluctant to wear the recorder at all times of day and night and it is not always easy in my experience to sort out ectopic rhythms from artifacts on the tapes It is because of these shortcomings that other diagnostic aids should be used in a condition which can prove difficult to diagnose because of its intermittent nature

The measures which I have described are admittedly not always successful but they sometimes are and they have the advantage of being easy to carry out. I quite agree that the patient in a Stokes Adams attack cannot feel his own pulse during the event but a witness can and it is a useful additional item that one can later extract from the witness s account In my experience most patients and their relatives find the instructions for taking the pulse easy to follow It seems unlikely that advising the patient to take his pulse would prove any more likely to provoke anxiety than the experience of being wired up to a Holter monitor

I certainly agree that full documentation of the arrhythmia should precede specific therapy whenever possible and as I noted in my article one should carefully balance the expected benefits of treatment against any likely iatrogenic complications

M E. Benaim, MB MRCP
Royal Victoria Infirmary
Newcastle upon Tyne
NE1 4LP
England

Value of the Balke protocol

To the Editor

The paper by Froehlicher and Lancaster in the April 1974 issue of the JOURNAL (87 445 450) warrants some comments. The authors rightly conclude that the maximal performance time in a continuous progressive treadmill protocol can only grossly predict maximal oxygen consumption They used the protocol first described by Balke and Ware in 1959 (reference 5) which specifies a fixed speed of walking of 3 3 m p h (90 m. per minute) with the gradient increasing 1 per cent each minute Of 1 025 men selected with an age of 34 2 ± 7 2 years weight and height unspecified and physical activity status not classified the correlation between V_{O_2} max and duration of exercise was only fair (r = +0 72) with S E E 4 26 ml/kg min) The best results were obtained in 127 men with multiple expired air bags collected." where correlation was appreciably better (r = +0 87) with S E E. reduced to 2 82 On comparison with sedentary younger middle aged men (36 3 ± 7 1 years) reported by Bruce and associates in this JOURNAL (85 546 562 1973) who were tested on a treadmill with both speed and gradient increased every three minutes (with a correlation between observed $\dot{V}_{O_2}$max and duration of exercise of r = +0 906 for sedentary men) the mean V_{O_2}max reported by Froehlicher and Lancaster was *only 88 per cent* and the maximal heart rate 98 per cent of the values found by Bruce and associates also the mean duration of exercise with the Balke protocol was *48 per cent longer* If compared with physically active subjects the disparity in V_{O_2}max would be even greater 49 7 ± 8 7 vs 36 15 ± 6 13 ml/(kg min)

These data strongly suggest systematic differences in results as well as in methods. Even though a multistage treadmill method was used the Balke protocol specifies a fixed speed, variable gradient with rapid but minor changes each minute before physiologic adaptation to the new load is fully achieved with respect to circulatory delivery of oxygen The total test takes significantly longer and 5 per cent of healthy men can even continue beyond the available 22 per cent gradient and 22 minute duration Of those who achieved maximal limits 22 per cent showed an absolute plateauing of oxygen uptake this corresponds to the 17 per cent reported by Bruce and associates in whom oxygen uptake reached a peak then fell slightly (−3 per cent) before exertion was stopped. Additional energy beyond aerobic supply for this effort, is derived from the rapidly depleted glycogen reserves in the skeletal muscles

In view of these differences the authors provide data suggesting that the Balke protocol is *not the most appropriate for clinical purposes.* Indeed, the moderately rapid speed *is too rapid* for older sedentary persons particularly if limited by cardiovascular impairments Finally the protocol is less practical for the busy physician because of the *greater time*

Letters to the Editor

Effect of acetylcholine on ventricular arrhythmias

To the Editor

It has long been known that acetylcholine can sustain fibrillation of the atrial muscles following electrical stimulation of the atrial wall in a heart lung preparation Atrial fibrillation persists as long as acetylcholine is infused This finding is in keeping with the electrophysiological properties of atrial muscles as shown by Hoffman and Suckling [1] who have shown that in dogs acetylcholine increases the rate of repolarization in the atria shortening the action potential more than tenfold However atrial fibrillation sustained by acetylcholine can be terminated by adding epinephrine into the infusion which is known to lengthen the action potential [2]

In summary the antifibrillatory effect of epinephrine on atrial muscles dominates the fibrillatory effect of acetylcholine However the effect of acetylcholine on ventricular muscles in initiating or terminating ventricular arrhythmias has not been shown in vivo An attempt has been made to study the effect of acetylcholine in ventricles in open chest dogs

The effect of acetylcholine on the left ventricle was studied in five open chest mongrel dogs by infusing the drug through the anterior descending branch of the left coronary artery

In these dogs acetylcholine was infused by a pump at the rate of 20 to 30 micrograms per minute through the anterior descending branch of the left coronary artery by a gauge 22 needle inserted through the left main coronary artery Simultaneous ECG His bundle electrogram and arterial pulse were monitored during this procedure The animals had phenobarbital anesthesia and left thoracotomy

While acetylcholine was being infused into the left anterior descending artery other pharmacological agents were infused into the jugular vein by an intracath Findings were very consistent First when acetylcholine was infused to the left anterior descending artery it produced retrograde V A block At first there was a ventricular standstill even though the atrium was beating at the normal sinus rate If the acetylcholine infusion was carried further both ventricular and atrial arrest occurred When acetylcholine was stopped before onset of the complete atrial and ventricular asystole the reversal of electrical activity was not similar in that atrial and ventricular activity did not resume in sequence and ectopic ventricular beats preceded the appearance of normal sinoatrial and ventricular conduction When atropine was infused systemically through the jugular vein at a rate of 200 μg per minute at the same time acetylcholine was being infused into the left anterior descending coronary artery the sequence of events did not change in that atropine did not make any difference to the electrical activity of the heart However if the acetylcholine infusion was stopped while the atropine infusion was continued the dog first developed sinus tachycardia followed by ventricular tachycardia and fibrillation This response to atropine could be abolished by pretreatment with Inderal intravenously in a dose of 2 mg per minute Similarly systemic isoprenaline infusion of 200 μg per minute did not have any effect on the ventricular rate so long as acetylcholine was being infused through the anterior descending coronary artery but ventricular tachycardia occurred when acetylcholine infusion stopped Atrial arrest following ventricular arrest occurred persistently and seemed to be due to recirculation of acetylcholine and its effect on the sinus node

Ventricular escape never occurred as long as acetylcholine was infused and His bundle potential always disappeared with ventricular asystole in the presence of atrial activity There is no way in which one can disprove that acetylcholine abolished Purkinje potential as well as His bundle potential even though the experiment was conducted without proper control as it is extremely difficult to carry out studies on intact animals particularly when using direct coronary profusion technique because of impending ventricular tachycardia and fibrillation The following inferences could be drawn to account for the appearance of ventricular ectopic activity

1 In the absence of enough catecholamine in the circulation the vagolytic effect of atropine would not be a major factor in the genesis of ventricular tachyarrhythmias

2 It is not the amount of acetylcholine in the circulation which prevents the appearance of ventricular ectopia but the ratio of catecholamine to acetylcholine in the circulation

3 Acetylcholine prevents the arrhythmogenic effect of catecholamine Recently an NIH group has shown that atropine may not be beneficial in the early phase of acute myocardial infarction as it may precipitate ventricular tachyarrhythmias [3] Perhaps the way atropine acts is by exposing the myocardium to an onslaught of catecholamine as it blocks the protective effect of acetylcholine This is probably very true in patients with myocardial infarction particularly with hypotension where enormous amounts of catecholamine are poured into the circulation Atropine may not be the real culprit in these situations but it surely helps catecholamine to produce the arrhythmia by preventing the protective effect of acetylcholine

It would appear that during the early phases of myocardial infarction increased vagal discharge[4] is provided by the autonomic nervous system to counterbalance the enormous catecholamine secretion and to offset this natural effect by drugs like atropine would not be beneficial

Debal Basu, M B.B.S F.R.C.P.C.
1800 Coffee Rd.
Modesto Calif 95355

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Value of Holter technique in arrhythmias

To the Editor

The annotation entitled Diagnosis of transient arrhythmias by M E Benaim in the April issue of this JOURNAL

(87 531 53?) requires additional comment Dr Benaim correctly emphasizes the clinical importance of transient arrhythmias and the benefit to the patient when a specific diagnosis can lead to specific treatment While it is helpful indeed if symptoms or attacks can be reproduced by the patient in the doctor s office or the patient is taught to continuously and accurately monitor his pulse rate and rhythm the inescapable evidence remains that the vast majority of patients escape detection unless a technique such as Holter monitoring is employed

Our experience with over 30 000 Holter tapes has revealed that the vast majority of clinically significant arrhythmias and conduction abnormalities are asymptomatic even in patients referred with a high index of suspicion It is also usual that patients with symptoms will have many similar episodes recorded that are not accompanied by subjective symptoms The patient with Stokes Adams syncope usually cannot feel his pulse during the event and elderly senile or anxious patients either cannot or should not be counting their pulse In addition the physician may be deprived of valuable or even critical information if the Holter technique is not employed. Ventricular extrasystoles may be close coupled multifocal paired, or in short salvos of ventricular tachycardia. ST segment changes suggestive of ischemia may occur Rate dependent conduction abnormalities may occur Arrhythmias or conduction abnormalities may occur during sleep

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Daniel J Bleifer M.D
Selvyn B. Bleifer M D
Harold L Karpman, M D
Cardiovascular Medical Group of Southern California, Inc
Beverly Hills Calif 90210

Reply

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M E. Benaim, M B M.R.C.P
Royal Victoria Infirmary
Newcastle upon Tyne
NE1 4LP
England

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In view of these differences the authors provide data suggesting that the Balke protocol is *not the most appropriate for clinical purposes.* Indeed the moderately rapid speed is *too* rapid for older sedentary persons particularly if limited by cardiovascular impairments Finally the protocol is less practical for the busy physician because of the *greater time*

required for testing healthy persons Whether the authors have identified some other advantages of the Balke protocol to offset these disadvantages is not apparent from this report

Robert A Bruce M D
Professor of Medicine
Co Director Division of Cardiology
School of Medicine
University of Washington
Seattle Wash. 98195

Reply

To the Editor

Dr Bruce s first comments refer to differences in the cor relation of V_{O_2} max to duration of exercise in two different treadmill protocols When the results at the USAF School of Aerospace Medicine using the Balke protocol were analyzed[1] and found to differ from the results of Bruce and his col leagues[2] the possibility that the Bruce protocol might be more suitable for predicting V_{O_2} max was considered Because of this possibility we have performed a study using two groups of approximately 80 subjects each with compara ble physical parameters and activity habits[3] One group was tested using the Bruce protocol and the other using the Balke protocol Regressing V_{O_2} max against duration of exercise yielded a correlation coefficient (r) of +0 87 and a S E E of 4 71 ml /(Kg min) for the Bruce protocol and a correlation coefficient of +0 80 and a S E.E of 3 95 ml /(Kg min) for the Balke protocol Also we have found that the duration of ex ercise in both protocols can increase with the number of times an individual is treadmill tested without an increase in V_{O_2} max[4] Thus there appears to be a wide range of V_{O_2} max for any exercise duration time Because of this wide range maximal performance time in both treadmill protocols can only grossly predict V_{O_2} max for a given individual

Another disappointing finding has been the wide range of maximal oxygen consumptions for normal subjects of any age measured by careful gas analysis.[5] Regressing V_{O_2} max on age in physical activity subgroups yielded a poor correla tion (r = −0 25 to −0 43) and a wide S E E (4 60 to 8 50 ml /(Kg min)[3] These findings make the nomogram for pre dicting functional aerobic impairment an uncertain clinical tool We suggest that before the prediction of functional aero bic impairment from exercise duration and age becomes an accepted clinical tool other investigators should validate it

In response to Dr Bruce s other comments we do not contend that the Balke protocol is the most appropriate treadmill protocol for clinical purposes It is used at the USAFSAM because of favorable experience with testing over 8 000 aircrewmen and because of its constant speed (3 3 m p h) which avoids motion artifact in the exercise elec trocardiogram common to other treadmill protocols which progress to faster speeds The electrocardiogram during exer cise is important to evaluate since we have found that 10 per cent of those with abnormal treadmill tests who develop CHD have ST segment changes during exercise alone[6] Cur rently we are evaluating a modified Balke protocol similar to that used by McHenry[7] It consists of a constant treadmill speed of 3 3 m p h three minute stages and 5 per cent grade increments per stage without limitation

Dr Bruce s enormous contributions to exercise testing are very apparent His comments and impetus to other investiga tors are very much appreciated

Dr V F Froelicher Major USAF MC
Dr A. J Thompson Major USAF MC
Clinical Sciences Division
School of Aerospace Medicine
Brooks AFB, Texas 78235

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The opinions expressed herein are those of the authors and cannot be construed as reflecting the views of the USAFSAM or the USAF

Experimental atrioventricular block by cutting the bundle branches

To the Editor

I am concerned with the histopathological evidence and arguments in the article Experimental atrioventricular block in the course of a hypocalcic electromechanical dis sociation Electrographic and histological data by Dorra Lardy Waynberger Grosgogeat and Bouvrain which ap peared in the February 1974 issue of the JOURNAL (87 190) It is reported that atrioventricular block was provoked in 10 isolated rabbit hearts perfused with hypocalcic solution by experimental cuts driven across the ventricular septum from the right side The return to sinus rhythm observed in four of these hearts on administration of normocalcic solution is held to represent quite a surprising and paradoxical phe nomenon of atrioventricular block regression. In turn, the in herent histological documentation shows that the septum had been severed about 5 mm. below the level of the Hisian bifurcation which makes it easy to infer that part of the con duction pathway might have escaped the experimental inter ruption

In my own experience from histological controls on dog hearts undergoing surgical section of either bundle branch[1,2] I happened to realize that procedures of this kind are some times inadequate and often unpredictable as to bringing about complete and lasting heart block and that atrio ventricular conduction impairments recorded in the acute phase of the experiment, may give way to sinus rhythm in a later stage Several cuts on both sides of the septum were needed to secure a chronic blockade of the atrioventricular pathway in the majority of cases

For instance in the heart illustrated in Fig 1 which ex hibits a pathological picture amazingly similar to that of case 2 of the quoted article the complete trans-eptal cut missed the right bundle branch and failed to interrupt atrio ventricular conduction



Fig 1 Complete cut (arrows) across the ventricular septum 5 mm below the Hisian bifurcation (*H*) not followed by atrioventricular block. (Hematoxylin and eosin ×24)

Altogether if one takes into account *these shortcomings* and pitfalls in any attempt at blocking the heart by severing both bundle branches, one finds very little to wonder about a supposedly paradoxical regression of the atrioventricular block in the four quoted cases, particularly upon restoration of a proper calcium level.

Lino Rossi, Lib Doc.Path.
Dir Lab of Histopathology
Columbus Clinic
20145 Milan Italy

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Reply

To the Editor

I thank Dr Rossi for his letter and for the interest he has shown in our article I would like to make the following comments in reply

1 I would like to point out that Dr Rossi s hypothesis is the first that comes to mind to explain the facts reported and was indeed the first quoted in our article (p 194 line 1 and following)

2 In fact, things are probably not so simple and there is presumably more than one explanation to these variations of atrioventricular conduction after an attempt at interrupting conduction pathways Now this is not of purely academic interest but also of great practical importance for the surgeon who tries to severe the Hisian pathway as a last resort in intractable and disabling supraventricular tachycardias

A Dr Rossi s experimentation is in fact not quite the same as ours. Dr Rossi apparently severes branches of the His bundle in the dog by *surgery* We on the contrary work on an *isolated* and perfused rabbit heart and we can therefore perform much more extensive cuts than can be done in *surgical* conditions

B Recurrences of sinus rhythm are well known and very preoccupying for cardiovascular surgeons who attempt to severe *not the branches but the His bundle* even while detected by its electrical activity [1]

C Sano and co workers [2,3] on the same material as ours (isolated and perfused rabbit heart) demonstrated three types of bypass tracts for atrioventricular conduction on the basis of electrophysiology[2] and histology [3]

It seems to us that the possible role of such pathways should be taken into account among other things whenever in animal or in man an atrioventricular block cannot be obtained by section of the conduction pathway in spite of all precautions.

3 We would like to stress that this was only one aspect of the discussion on the facts we published. The main point was to give an experimental demonstration that during hypocalcic electromechanical dissociation and in certain very definite concentrations of the perfusion in $CaCl_2$ it was possible on a heart in complete arrest to record not only a persistent electrical activity but also the disorders of excitability or conduction which could be observed on a heart beating normally

Prof Agregé Max Dorra
Service de Medecine Interne
Hopital Ambroise Pare
92 Boulogne France

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Book reviews

The Mammalian Myocardium Edited by Glenn A Langer and Allan J Brady New York 1974 John Wiley & Sons Inc 310 pp $24 50

Langer and Brady have edited a very good book on the myocardium The contributors are experts in their respective fields Although the book contains only 300 pages the quality of the illustrations and the respective chapters are concise and relevant The chapters include discussions of ultrastructural contractile proteins active transport energetics mechanics electrophysiology ion exchange adrenergic mechanisms coronary circulation, and myocardial failure It is the heart muscle which sustains the circulation and life It is the most important functioning part of the heart. This book therefore should interest all medical students and doctors and certainly cardiovascular physiologists and physicians

Cardiac Arrhythmias By Stelio Mangiola M D and Michael Ritota M D Philadelphia 1974 J B Lippincott Co 215 pp $22 00

This manual contains very clear illustrations of a large assortment of ECG of arrhythmias It is a good practice source from which much can be learned The explanations associated with the interpretations are of value to beginners

Symposium on Cardiac Arrhythmias American Heart Association Monograph No 40 Edited by Ephraim Donoso M D American Heart Association 1974 214 pp $5 00

This monograph on cardiac arrhythmias is a good one It includes ultrastructural anatomy and electrophysiology as they pertain to arrhythmias Specific relatively common disturbances in cardiac rhythms are presented This is a good discussion of the arrhythmias of the heart. Students and physicians will find this to be a very good monograph

Noninvasive Cardiology Edited by Arnold M Weissler M D New York and London 1974 Grune & Stratton Inc 454 pp

This book edited by Weissler is concerned with noninvasive" procedures used in cardiology It is a mistake however to consider procedures that do not require intravascular or intracardiac manipulation or procedures as the only or even the most important aspects of noninvasive cardiology The practice of cardiology for decades has been noninvasive The history and physical examination as well as routine laboratory studies such as roentgenography and electrocardiography are noninvasive These approaches the most fundamental of all studies, are not even considered in this book To correct this the editor merely needs to modify the title

This book includes a series of chapters on such special procedures as apexcardiography ballistocardiography echocardiography kinetocardiography radarkymography systolic time intervals nuclear cardiology and external venous and arterial pulses These procedures are rarely used by the doctors of the world They are available in the large centers where investigators have special interests and usually research interests.

This book is of value and interest to specialists in cardiology The chapters summarize very well these respective fields of cardiology The illustrations and presentations are clearly presented For those who wish to study and learn these various procedures this book is an available single source

Clinical Cardiac Radiology By Keith Jefferson and Simon Rees Toronto 1973 Butterworth & Co Ltd 314 pp $57 75

This is an excellent book on cardiac radiology It is based on a study of over 1 500 patients, not only with autopsy correlations but also with clinical cardiac catheterization physiologic and other data The book is intended for clinicians in the practice of medicine who treat patients with heart disease The authors correlate clinical and physiologic data with the x ray findings very effectively and in a practical manner The book is divided into two parts The first part is concerned with general radiology and the second part with the clinicoradiologic approach to heart disease The grouping of chapters is done to simplify the presentation of the radiologic manifestations of heart disease The illustrations are well selected and the text clearly written This book should provide much useful practical information to students general physicians and cardiologists The authors have produced a good book on an important subject

Cardiac Arrhythmias. Basic Concepts and an Approach to Self Instruction By Louis Rakita M D and Martin I Broder M D Cleveland, 1974 The Case Western Reserve University Press 192 pp

This manual is designed for self teaching and self assessment on cardiac arrhythmias The manual is designed as others of this type for the readers to study actual tracings and illustrations and then to answer questions listed This is a conventional type of study and self assessment manual

Books received

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Progress in Hemostasis and Thrombosis Vol 2 Edited by Theodore H Spaet MD New York, 1974 Grune & Stratton, Inc 373 pp Price $22 50

The Human Fetal and Neonatal Circulation Function and Structure By S Zoe Walsh MD W W Meyer MD and John Lind MD Springfield, Ill 1974 Charles C Thomas Publisher 351 pp Price $15 00

Health Education Theory and Practice in Cancer Control A Collection of Original Papers—1974 Presented by the Committee on Public Education of the International Union Against Cancer Technical Report Series vol 10 available from the Managing Editor International Union Against Cancer 3 rue du Conseil General 1205 Geneva Switzerland. Individual copies free orders for 5 or more 3 Swiss francs per copy

Announcements

Refresher course in cardiac radiology

A refresher course in cardiac radiology will be held by the North American Society for Cardiac Radiology from March 2 to 6 1975 in Williamsburg Va A distinguished faculty will conduct seminars covering the radiology of acquired and congenital heart disease and its clinical implications For further information please write to Klaus Ranniger M D Medical College of Virginia MCV Station Box 2 Richmond Va 23298

Twelfth Annual Cardiology Seminar

The twelfth annual cardiology seminar sponsored by The Rogers Heart Foundation will be held at the Melia Castilla Hotel Madrid Spain, from Oct 31 1974 through Nov 7 1974 The seminar directed by Henry J L Marriott M D will have as faculty Charles Dubost M D Paris Dirk Durrer M D Amsterdam Ronald Gibson F R C P London Richard Gorlin M D New York Frank LaCamera Jr M D St. Petersburg Henry J L Marriott M D St Petersburg Col William P Nelson M D Denver J Graeme Sloman F R C P Melbourne Demetrio Sodi Pallares M D Mexico City H J Swan M D Los Angeles Edward J Swanick M D St Petersburg and Arnold Van Lier M D Rotterdam

Transportation will be via a chartered Iberia Air Lines of Spain Jumbo 747 leaving John F Kennedy International Airport, New York on or about Oct. 31 for Madrid and returning to the same airport on Nov 7 Travel costs and accommodations (double occupancy) will be approximately $309 (U.S) per person Registration fee for the seminar is $50 with a $100 tuition fee payable later For further information please write The Rogers Heart Foundation St. Anthony s Hospital St Petersburg Fla 33705 or telephone (813) 894 0790

Seminar on intra aortic balloon pumping

A seminar entitled Concepts of Intra Aortic Balloon Pumping An Interdisciplinary Approach" will be held in Boston Mass. on November 1 and 2 1974 Sponsored by the Massachusetts General Hospital Departments of Cardiology Cardiovascular Surgery and Nursing the seminar will be held in Shriners Burn Institute Auditorium Boston Mass

For further information regarding this seminar please contact Ms H Chapin Department of Continuing Education Harvard Medical School 25 Shattuck St Boston Mass 02115

American Heart Journal

November 1974 Volume 88 Number 5

Editorial

Exercise training the myocardium, and ischemic heart disease

Lionel H Opie M D

Cape Town, South Africa

Does exercise training really have a role in the prevention and treatment of ischemic heart dis ease? There is good evidence that exercise may alter the myocardial response to hypoxia Scheuer and colleagues[1,2] have shown that iso lated hearts from rats exercised by a regular swimming program have improved function of the heart as a pump in response to atrial pacing increased atrial filling pressure and hypoxia The biochemical mechanisms involved include increased actomyosin ATPase activity[3] which is generally correlated with increased contractility of the heart In wild animals (e g the hare) the heart is not only larger but the capillary network is denser than in the closely related nonexercis ing tame rabbit[4] There has recently been a detailed review on the effects of chronic exercise on the cardiovascular system and on the athero genic process by Froelicher[5] who concluded that exercise improved the capacity of the heart to withstand stress but that data suggesting that the actual atherosclerotic process could be affected were only suggestive

Exercise may also influence the coronary blood flow In hearts from sedentary rats the coronary blood flow fails to increase significantly during mechanical stress while the increased mechani cal response in perfused hearts from exercise conditioned animals appears to be related to an improved coronary flow rate[1]

The effects of exercise on the myocardium are not always beneficial or clear cut For example over exercised rats develop degenerative cardiac changes which are prevented by the administra tion of digitoxin compounds[6] Heavily exercised rats fail to develop the expected increase in size of the coronary tree as measured by a cast tech nique[7] Some workers have failed to show in creased values of mitochondrial protein or of respiratory enzymes in the myocardium of exer cised rats and have suggested that the capacity for aerobic metabolism of a normal untrained rat heart is adequate to meet the increased demands for ATP by exercise[8,9]

None of the above data prove that exercise training can alter the development of ischemic heart disease or help patients with established coronary artery disease However recent reports on the use of exercise in diminishing the inci dence and severity of angina pectoris have been promising The mechanism of response of angina to exercise training might involve reductions in the reactions of the heart rate and the arterial pressure to exercise possibly enhanced myocar dial oxygen delivery[10] and a decreased cardiac

From the Ischaem c He rt Dise se Labora ory Department of Medi ci Unive rsity of Cape T w Cape T wn, South Africa

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Reprint requests to Dr Lionel H. Opie Ischaemic H rt Disease Labor tory Department of Medicine University of Cape Town, Cape T wn, So th Africa.

output for a given amount of exercise[11] In normal subjects exercise increases the fibrinolytic activity of the blood,[12] but this mechanism was excluded in the study by Redwood, Rosing and Epstein[10] The placebo effect of exercise must certainly not be ignored[13] because an exercise program involves the patient with frequent contact with trainer and physician, and the impression is created that something important is being achieved There is also suggestive evidence that a training program diminishes the frequency of premature ventricular complexes induced by acute exercise[14] At least some of the above effects are consonant with the suggestion of Raab and colleagues[15] that exercise may act by decreasing cardiac adrenergic overactivity

Exercise training can improve the claudication distance in patients with peripheral vascular disease[16] If it be accepted that the pain of intermittent claudication is similar in its pathogenesis to that of angina pectoris then the effects of exercise on intermittent claudication also argue for exercise training in patients with angina pectoris Exercise training in man is accompanied by metabolic alterations in peripheral muscle[17], there are increments in the size and oxygen uptake of peripheral muscle mitochondria as well as in the overall tissue contents of glycogen, glycogen synthetase and hexokinase[18] Similarly in the gastrocnemius of exercised rats there is increased activity of some aerobic enzymes such as succinic oxidase and dehydrogenase, cytochrome oxidase an increased concentration of cytochrome C and enhanced mitochondrial capacity for electron transport and manufacture of ATP[19]

Exercise programs have also been used to help rehabilitate patients after myocardial infarction According to Hansen[0] it has been shown that some patients with coronary artery disease can be trained so that daily activities can be performed without symptoms, physical training is also a stimulus to the patient to live through the postinfarction period with greater confidence Exercise is not without dangers and the physician advising exercise as either a therapeutic or diagnostic procedure has definite medicolegal responsibilities[21] The presence of emergency defibrillation equipment during training sessions is held to be essential by some workers,[22] because sudden death has been associated with vigorous exercise in subjects with coronary artery disease[23] However, treadmill tests three weeks after the onset of acute infarction may help to separate patients prone to arrhythmias from other patients[24]

How much exercise is needed? Because of the similarity in the metabolic changes induced by exercise and by intermittent hypoxia it may be that tissue hypoxia is required for the adaptive changes of exercise[25] In human skeletal muscle, the degree of breakdown of phosphocreatine is increased by the magnitude of the work load[26] Even 90 minutes of swimming exercise in the rat produces enlarged heart mitochondria[27] and less than one minute of much increased heart work decreases the high energy phosphate content of the isolated perfused rat heart[28] In healthy man, the degree of exercise should be such as to produce a high heart rate, higher rates are associated with an increased training effect[29] Epidemiologic data suggest that the heart rate should be raised to a maximum to protect from ischemic heart disease[30]

The minimum amount of exercise suggested by Kilbom[31] is half an hour of submaximal exercise three times per week, supplemented with running and jogging and using stairs instead of the elevator[29] In healthy people, improved fitness is lost within two weeks of cessation of exercise but half an hour every fourth day can maintain the training effect[29] In middle aged men, an exercise program of one hour per day for three days per week could significantly improve treadmill performance and favorably change some of the risk factors for ischemic heart disease, fitness could be maintained on as little as one strenuous 30 minute session per week[32] Three half hour sessions per week could improve the fitness of patients convalescing from myocardial infarction[33] In patients with angina, exercise was carried on to the point of pain (after the administration of nitroglycerin) twice a day for five days a week with good results[10]

The concept that exercise plays a role in the prevention of ischemic heart disease fits well with epidemiologic data suggesting that physical activity at work or leisure protects against the development of ischemic heart disease[30,34] and with Raab's concept of the "loafer's heart"[35] It has not yet been proved that increased exercise in any given individual would diminish the risk of development of ischemic heart disease although this would at present appear to be a reasonable supposition

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Clinical communications

The assessment of the arterial supply to the lungs in pseudotruncus arteriosus and truncus arteriosus Type IV in relation to surgical repair

Elliot Chesler, M D , F R C P E , F A C C *
Rodney Matisonn M B , Ch B , F C P (S A)*
Walter Beck M Sc , M Med F R C P , F A C C
Cape Town South Africa

Of those congenital cardiac malformations resulting in cyanosis truncus arteriosus and pseudotruncus arteriosus are characterized by the fact that the entire blood supply to the lungs is derived from the aorta rather than by direct connection to the heart The advent of surgical techniques whereby a conduit from the left or right ventricles to the pulmonary arteries may be established has made it important to recognize those cases potentially suitable for surgical correction [1] The spectrum of these abnormalities has recently been reviewed in detail from the anatomic point of view [2]

Patients with truncus arteriosus Types I through III infrequently present with continuous murmurs and angiograms demonstrate pulmonary arteries arising singly, or as a common trunk from the ascending aorta The most difficult differentiation is between truncus arteriosus Type IV and pseudotruncus arteriosus where widespread continuous murmurs arise from collateral vessels from the arch or descending portions of the aorta In this report we deal specifically with the nature of the blood supply to the lungs in these two conditions and the frequency with which these cases are amenable to surgical correction

Materials and methods

Forty four patients were studied Their ages were as follows 1 month to 1 year (11 cases), 1 year to 5 years (5 cases), 5 years to 10 years (13 cases), 10 years to 15 years (5 cases) 15 years to 20 years (6 cases) 20 years to 25 years (3 cases) and 31 years (1 case)

Twenty two patients were males and 22 were females Although we have encountered several examples of pulmonary atresia associated with a single ventricle or with tricuspid atresia, these were excluded from the present study because at the present time full surgical correction is not available

The physical findings were virtually uniform in all patients Apart from one case cyanosis was always present and there was never any evidence of congestive cardiac failure There was clinical evidence of right ventricular hypertrophy and auscultation disclosed a single second sound of aortic valve closure In all but one patient, wide spread continuous murmurs were present and these were frequently heard better on one side of the chest an aortic ejection click was often detected

Roentgenograms of the chest showed a cardiac silhouette similar to that of tetralogy of Fallot with a prominent aortic arch a well marked concavity in the region of the pulmonary artery segment as well as right ventricular enlargement Excluding the one patient who was acyanotic the lung fields were undervascularized frequently unequally so although in many patients it was possible to distinguish both pulmonary arteries The electrocardiograms showed right axis deviation and right ventricular hypertrophy and were very similar to those electrocardiograms observed in tetralogy of Fallot except in two instances where there were conduction defects one case with right bundle branch block had an associated atrial septal defect and the other case

From the Cardiac Clinic Groote Schuur Hospital, and the Department of Medicine University of Cape Town Cape Town South Africa
Received for publication Nov 27 1973
Reprint requests Cardiac Unit, Wentworth Hospital P B Jacobs Natal South Africa
Present address Cardiac Unit, Wentworth Hospital P B Jacobs Natal, South Africa

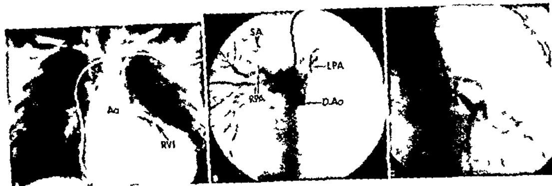


Fig 1 Pseudotruncus arteriosus A, right ventricular angiogram (frontal view showing blind right ventricular in fundibulum (RVI) and a systemic collateral vessel (SA) B selective catheterization showing bilateral hypoplasia of confluent pulmonary artery branches (LPA and RPA) A collateral vessel (SA) supplies the right lower lobe C selective catheterization of independent collateral vessel to left lower lobe which has stenotic segment (arrow heads) Ao = aorta DAo = descending aorta

with left axis deviation and right bundle branch block had an endocardial cushion defect.

Right side cardiac catheterization was performed in standard manner and pulmonary and systemic blood flows were measured by the Fick technique in all cases except in severely ill children where a systemic blood sample was not obtained Oxygen uptake was determined directly in the adults or from predicted values in the children In most patients it was not possible to obtain a pulmonary venous sample and this was assumed to be fully saturated at 97 per cent. Right ventricular biplane angiography revealed a single vessel leaving the heart and delayed opacification of the pulmonary vasculature from the aorta particular attention was paid to the anatomy of the right ventricular outflow tract. The blood supply to the lungs was studied as follows of the 28 patients above the age of 5 years, 24 cases (86 per cent) were studied by selective catheterization of these vessels and 23 cases through an arteriotomy (brachial 21 cases femoral 2 cases) and pressures and selective angiograms obtained by a previously described technique[3] In the other patient selective catheterization was performed from the venous route traversing the ventricular septal defect into the aorta The remaining four cases had aortography alone Of the 16 patients below the age of 5 years selective catheterization was not used at all aortography was performed in 10 cases and in six patients under one year of age the aortic blood supply to the lungs was carefully observed following right ventricular cineangiography exposed at 64 frames per second.

On the basis of these angiographic features the material was divided into two groups depending whether pulmonary arteries were recognized or not In those cases where the main or the left and right branches of the pulmonary artery were identified to the hila of the lungs an assessment was made in relation to potential surgical correction on the basis of their size distribution and continuity When connected across the midline they were regarded as *confluent* and when they arose independently of each other they were regarded as *nonconfluent* according to the classification of Edwards and McGoon[2] In addition their source of blood supply was identified as either a patent ductus arteriosus or as systemic arteries arising from the aortic arch or the descending aorta. These systemic connections were classified according to their size and whether they were stenotic or not A similar procedure was employed in those cases where no elements of the sixth arch were identified Some attempt was made to assess pulmonary vascular resistance from hemodynamic data

Results

The various angiographic and hemodynamic data are described in Table I The great vessels were normally related in 41 cases (93 per cent) and transposed in three cases The aorta was right sided in 7 cases (16 per cent)

Group A pulmonary arteries demonstrated—38 cases (86 per cent) (Figs 1 through 4)

Operable group—29 cases (76 per cent) Twenty six patients with confluent pulmonary arteries were judged to be potentially suitable for complete correction and in four cases the main pulmonary artery was present. Four of these pa

The assessment of the arterial supply to the lungs in pseudotruncus arteriosus and truncus arteriosus Type IV in relation to surgical repair

Elliot Chesler, M D, F R C P E, F A C C*
Rodney Matisonn, M B, Ch B, F C P (S A)*
Walter Beck, M Sc M Med, F R C P, F A C C
Cape Town South Africa

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From the Cardiac Clinic Groote Schuur Hospital and the Department of Medicine University of Cape Town Cape Town South Africa.

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Reprint requests Cardiac Unit, Wentworth Hospital, P B Jacobs Natal South Africa

*Present address Cardiac Unit, Wentworth Hospital P B Jacobs Natal South Africa

Table I Tabulation of hemodynamic and angiographic data observed in 44 cases studied

Case No.	Age (yrs)	Sex	Relationship aorta to PA	Aortic arch	Blind RVI	Blood supply to lungs			
						MPA	LPA	RPA	Confluence LPA and RPA
Group I Pulmonary arteries demonstrated									
1	6	M	N	L	+	–	+	+	+
2	5	M	N	L	+	+	+	+	+
3	6	F	N	L	+	–	+ Absent LLL	+	+
4	7	F	N	L	+	–	+ Absent LLL	+	+
5	15	M	N	L	+	+	+	+	+
6	13	M	T	L		–	+	+	+
7	9	M	N	L	+	–	+	+	+
8	1	F	N	L	+	–	+	+	+
9	1	F	N	L	+	–	+	+	+
10	2/12	F	N	L	+	–	Hypoplastic	Hypoplastic	–
11	17	M	N	R	+	–	+	+	+ Stenotic orig ns
12	25	M	N	L	+	–	+	+	+ Stenotic origins
13	6	M	N	L	+	–	Hypoplastic absent RLL	Hypoplastic absent LLL	+
14	1/12	F	N	L	+	–	Hypoplastic	Hypoplastic	–
15	3/12	F	N	L	+	–	+	+	+
16	7/12	M	N	L	+	–	+	Hypoplastic	+
17	15	M	N	R	+	–	+	+	+ Stenotic origins
18	7	F	N	L	+	–	+	Hypoplastic	+ Stenotic origins
19	11	F	T	L		+	–	+	–
20	5	F	N	R	+	–	Hypoplastic	Hypoplastic	+
21	7	F	N	L	+	+	+	+	+
22	4/12	F	T	L		–	Hypoplastic	Hypoplastic	–
23	16	F	N	R	+	–	–	+	+
24	3/12	M	N	L	+	–	+	+	+
25	2/12	M	N	L	+	–	+	+	+
26	5	M	N	L	+	–	Hypoplastic	Hypoplastic	+
27	7/12	F	N	L	+	–	+	+	+
28	7	F	N	L	+	–	+	+	+
29	7/12	F	N	L	+	–	+	+	+
30	7	F	N	L	+	–	+	+	+
31	6/12	M	N	L	+	–	+	+	+
32	2	F	N	L	+	–	+	+	+
33	5	M	N	R	+	–	+	+	+
34	20	F	N	L	+	–	Hypoplastic	–	–
35	13	F	N	L	+	–	–	+ Except RUL	–

D Ao descending aorta LPA and RPA = left and right pulmonary arteries respectively LLL = left lower lobe

Blood supply to lungs							
PDA	Systemic artery	Stenosis PDA or systemic artery	PAP (mm. Hg)	PVR (units)	QP/QS	O_2 Sat (%)	Operability
–	D Ao to LLL	+	?	?	2 9/3 8	76	Yes
	D Ao to LPA and RPA (small)	+	12/10	12	3 6/4 9	73	Yes
+	–	–	?	?	8 9/6 3	85	Completely repaired
Previous Blalock	–						
–	D Ao to both lungs multiple and large	–	?	?	3 3/4 9	73	No
–	D Ao to both lungs multiple and large	+ Intrahilar	?	?	7 2/3 3	86	No
–	D Ao to R lung (2) (large)	–	?	?	11 3/3 9	84	No
	D Ao to L lung (1) (large)	+ Intrahilar	?	?			
–	D Ao to both lungs multiple and large	+ Intrahilar	?	?	0 9/2 2	70	No
–	D Ao to both lungs (small)	+	?	?	3 5/9 3	72	No
–	D Ao to R lung (large) and L lung (small)	–	120/78	12	2 8/5 5	83	No

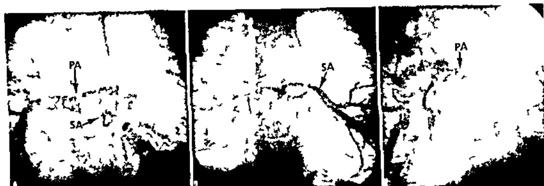


Fig 3 Pseudotruncus arteriosus A and C frontal and lateral views respectively showing confluent pulmonary arteries (PA) supplied by a small stenotic systemic vessel (SA) B, selective injection into systemic vessel supplying L midzone An intercostal vessel on right is also opacified (arrow) The systemic vessel is stenotic and supplies the area of lung not fed by the left pulmonary artery (cf A)

small restrictive systemic vessel with Qp < Qs In three cases the pulmonary arteries were supplied by a patent ductus arteriosus as well as a small systemic vessel both restrictive angiographically and with Qp < Qs In two patients the nature of the collateral blood supply could not be assessed because a previous Blalock Taussig operation had presumably obliterated these vessels. In one patient who underwent successful repair using a homograft and where there was more than one collateral blood supply to the lungs the systemic vessel supplying a small area of the lung was not ligated and the patient was left with a soft continuous murmur It is of interest to note that in this and other cases these small systemic vessels provided an additional source of blood supply distal to an area of stenosis in one of the branches of the pulmonary artery

Inoperable group—nine cases (24 per cent) The main pulmonary artery was not identified in any of these cases. In four cases the pulmonary arteries were confluent but markedly hypoplastic

Table I continued

Case No.	Age (yrs)	Sex	Relationship aorta to PA	Aortic arch	Blind RVI	Blood supply to lungs			
						MPA	LPA	RPA	Confluence LPA and RPA
Group I Pulmonary arteries demonstrated									
36	13	F	N	L	+	–	+ Except LLI	+	+
37	15	M	N	L	+	–	+	+	+
38	30	M	N	L	+	+	+	+	+
Group II Pulmonary arteries not demonstrated									
39	7/12	M	N	L	–	–	–	–	–
40	3	M	N	R	–	–	–	–	–
41	3	F	N	R	–	–	–	–	–
42	18	F	N	L	–	–	–	–	–
43	25	M	N	L	+	–	–	–	–
44	10	F	N	L	+	–	–	–	–

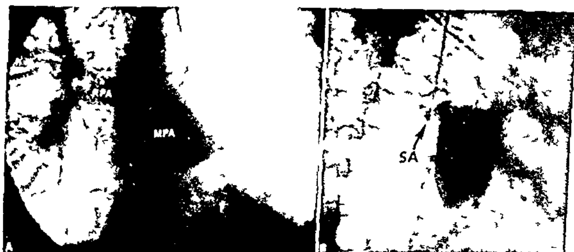


Fig 2 Selective catheterization of pulmonary artery via a stenotic systemic vessel (SA) in a case of transposition of the great vessels pulmonary atresia and ventricular septal defect *A* frontal and *B* lateral views respectively The left pulmonary artery is absent and the left lung is supplied by extensive collateral supply demonstrated by other selective studies

tients had angiographic evidence of mild stenosis of the origins of the pulmonary arteries which would constitute no surgical problem

In addition, another three patients had a normal pulmonary artery supplying one lung only and supplied by a restrictive patent ductus arteriosus in one case a shunt procedure was carried out These three patients could also be treated by a homograft conduit in the same way as those cases of tetralogy of Fallot with absence of one pulmonary artery

The *source of blood supply* to the pulmonary arteries in this group was a patent ductus arteriosus alone in 20 cases in 17 cases the ductus was restrictive with Qp < Qs and in three cases where the ductus was nonrestrictive the Qp/Qs was more than 2/1 In four cases the blood supply to the pulmonary arteries was derived

Blood supply to lungs							
PDA	Systemic artery	Stenosis PDA or systemic artery	PAP (mm Hg)	PVR (units)	QP/QS	O_2 Sat (%)	Operability
–	D Ao to LLL	+	?	?	2 9/3 8	76	Yes
	D Ao to LPA and RPA (small)	+	12/10	12	3 6/4 9	73	Yes
+	–	–	?	?	8 9 6 3	85	Completely repaired
Previous Blalock	–						
–	D Ao to both lungs multiple and large	–	?	?	3 3/4 9	73	No
–	D Ao to both lungs multiple and large	+ Intrahilar	?	?	7 2/3 3	86	No
–	D Ao to R lung (2) (large)	–	?	?	11 3/3 9	84	No
	D Ao to L lung (1) (large)	+ Intrahilar	?	?			
–	D Ao to both lungs multiple and large	+ Intrahilar	?	?	0 9/2 2	70	No
–	D Ao to both lungs (small)	+	?	?	3 5/9 3	72	No
–	D Ao to R lung (large) and L lung (small)	–	120/78	12	2 8/5 5	83	No



Fig 3 Pseudotruncus arteriosus *A* and *C* frontal and lateral views respectively showing confluent pulmonary arteries (PA) supplied by a small stenotic *systemic vessel* (SA) *B*, selective injection into systemic vessel supplying L midzone An intercostal vessel on right is also opacified (arrow) The systemic vessel is stenotic and supplies the area of lung not fed by the left pulmonary artery (cf A)

small restrictive systemic vessel with Qp < Qs In three cases the pulmonary arteries were supplied by a patent ductus arteriosus as well as a small systemic vessel both restrictive angiographically and with Qp < Qs In two patients the nature of the collateral blood supply could not be assessed because a previous Blalock Taussig operation had presumably obliterated these vessels. In one patient who underwent successful repair using a homograft and where there was more than one collateral blood supply to the lungs the systemic vessel supplying a small area of the lung was not ligated and the patient was left with a soft continuous murmur It is of interest to note that in this and other cases these small systemic vessels provided an additional source of blood supply distal to an area of stenosis in one of the branches of the pulmonary artery

Inoperable group—nine cases (24 per cent) The main pulmonary artery was not identified in any of these cases In four cases the pulmonary arteries were confluent but markedly hypoplastic



Fig 4 Pseudotruncus arteriosus Selective catheterization of confluent pulmonary arteries (PA) *A* showing deficient supply to left lower lobe which is supplied by a separate systemic vessel (SA) demonstrated in *B*



Fig 5 Truncus arteriosus Type IV *A B* and *C* frontal views showing selective catheterization and angiography of large nonobstructive systemic vessels arising from a right sided descending aorta supplying both lungs (See text)

(Fig 1) in the remaining five cases the pulmonary arteries were nonconfluent hypoplastic and the source of blood supply to the lungs was systemic The *source of blood supply* in this group was a patent ductus arteriosus alone which was restrictive (one case) systemic alone (restrictive two cases nonrestrictive four cases) and a combination of patent ductus arteriosus and systemic vessels two cases (one restrictive patent ductus and one restrictive systemic vessel) It is to be emphasized that of the five patients with absent or hypoplastic nonconfluent pulmonary arteries two were aged one and two months respectively Both patients are doing well and it is possible that, with the passage of time their pulmonary arteries may enlarge sufficiently for them to become surgical candidates

Ventricular anatomy In three cases in Group A where the great vessels were transposed the right ventricular infundibulum was normally developed In the remaining 35 cases the infundibular chamber was blind usually grossly hypoplastic foreshortened, situated on the upper left cardiac border and orientated from left to right (Fig 1)

Group B pulmonary arteries not demonstrated—six cases (14 per cent) (Figs 5 and 6) In this group the blood supply to the lungs was derived from the descending aorta and no elements of the main left or right pulmonary arteries were identified by angiography

Surgery was precluded on anatomic grounds alone in these six cases. Although these vessels were large their site of origin and multiplicity would make homograft insertion technically impossible In any event the frequency of intrahilar stenosis of the intrapulmonary arteries or of hypertensive arteriolar changes in those cases without stenosis would leave a situation with a potentially high vascular resistance even if surgery could be accomplished

Ventricular anatomy Of the six cases in Group

B a blind hypoplastic infundibulum was iden tified in two instances

Surgical experience

At the present time our surgical experience with total correction embraces seven cases all of whom had confluent pulmonary arteries in six cases an aortic valve homograft was inserted into the right ventricular outflow tract and anasto mosed to the pulmonary arteries and the ventric ular septal defect closed. In the seventh case the fibrous diaphragm separating the infundibulum from the main pulmonary artery was merely in cised and the patient left with a degree of pul monic insufficiency no worse than that occurring so commonly postoperatively in tetralogy of Fallot. One patient with similar anatomy and a restrictive patent ductus underwent a shunt pro cedure at the age of three months. We have not encountered a case suitable for surgical correc tion with an absent right ventricular outflow tract where the collateral blood supply to the lungs was amenable to correction on hemody namic or anatomic grounds

Comment

Truncus arteriosus Type IV[4] (absent sixth arch)[5] and pseudotruncus arteriosus[6] (pulmonary atresia with ventricular septal defect) are well defined malformations although considerable se mantic confusion exists as to the best terminolo gy to be used in their description[7,9] However it is not the purpose of this report to attempt clarification of this issue but rather to identify those cases suitable for surgical correction On the basis of our findings we feel that there are certain helpful pointers in this regard which are compatible with the pathologic anatomy and cur rently understood embryology

The pathologic anatomy and embryology of pulmonary atresia with normally related and transposed great vessels has been well delineated by Munoz Armas and co workers[10] In this condi tion there are varying degrees of development of the components of the sixth aortic arch (left and right pulmonary arteries and the ductus ar teriosus) and unequal partitioning of the trun cus conus occurs at the expense of the main pul monary artery pulmonary valve and the sub pulmonary infundibulum. Whereas the branches of the pulmonary arteries originate from the sixth aortic arch, the main pulmonary artery is

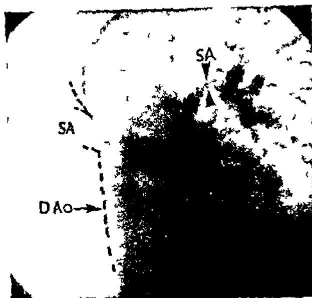


Fig 6 Truncus arteriosus Type IV frontal view showing selective catheterization and angiography of systemic vessels (SA) arising from a right sided descending aorta The vessel to the left lung has an area of intrahilar stenosis (arrow heads) The large vessel to the right lung is opacified by reflux and is nonobstructive (See text)

formed by division of the truncus arteriosus and pulmonary valve and trunk atresia may occur with reasonably developed left and right pulmo nary artery branches In cases with transposition of the great vessels there is abnormal rotation of the trunco conal ridges they emerged in a straight manner and after fusion form a straight trunco conal septum This makes the pulmonary artery branches take a sinistrodorsal position and communicate with the anatomic left ventri cle whereas the aorta occupies a dextroventral position and communicates with the right ventri cle[10]

In truncus arteriosus Type IV there are no derivatives of the proximal portions of the ven tral sixth aortic arch the main pulmonary ar tery and the right ventricular infundibulum is absent because the sinistroventral conus ridge has not developed and the dextrodorsal conus ridge is deficient in that portion which gives rise to a part of the ventricular septum[11]

In both conditions the blood supply to the lungs is derived primarily from the postpulmonary branchial plexus which arises from the esophage al region as the lungs develop Normally union of the postpulmonary branchial plexus with the ventral elements of the sixth arch establishes the normal circulation On the right side the dorsal

segment of the sixth arch disappears and the ventral bud in continuity with the postpulmonary plexus forms the right pulmonary artery On the left side the dorsal portion of the sixth arch persists as the ductus arteriosus while the ventral portion in continuity with the postpulmonary plexus forms the left pulmonary artery [12,14]

In pseudotruncus arteriosus, the sixth arch may be supplied by a patent ductus, vessels from the arch or descending portions of the aorta, or both Difference of opinion exists as to whether these vessels represent true bronchial arteries or not [15] In truncus arteriosus Type IV, inasmuch as the ventral portion of the sixth arch is absent, the blood supply to the lungs is from the descending aorta [16] However, as recently pointed out by Murray and co workers [14] a ductus may be present in this anomaly when the dorsal portion of the sixth arch persists and unites with the postpulmonary plexus, while its ventral component, the precursors of the left and right pulmonary arteries, are absent

Our observations from our clinical material would be in concert with these embryologic concepts but at variance with some aspects of other clinical studies of these conditions Thus of our 44 cases a right ventricular infundibulum was identified angiographically in 40 patients and elements of the sixth arch were identified in 38 patients (95 per cent), in at least 29 cases (76 per cent) the anatomy of the pulmonary arteries was suitable for surgical repair In the remaining two cases, elements of the sixth arch were not identified and the blood supply to the lungs was from aortic collateral vessels only Necropsy in one of these cases showed extreme hypoplasia of the main pulmonary artery and both of its branches were represented by fibrous cords, a very large collateral vessel from the descending aorta supplied the right lung Transposition of the great vessels was present in three cases (7 5 per cent) of this group, and this low incidence is in keeping with the pathologic study of Muñoz Armas and co workers[10] and their review of the literature on this subject These 40 cases are regarded as examples of pseudotruncus arteriosus

Of the four cases where a right ventricular infundibulum was not recognized angiographically and which we regard as probable examples of truncus arteriosus Type IV, elements of the sixth arch were not identified and none of these cases would have been suitable for surgical repair because the collateral vessels from the descending aorta were multiple thus excluding surgery technically and also for hemodynamic reasons because of the frequency of intrahilar stenosis Our series of truncus arteriosus Type IV is small but the features correspond to published studies of the pathologic anatomy of this condition Also it is noteworthy that there are only four reported cases of surgical repair of this anomaly, in all of the cases there were large vessels supplying at least one lung and the hemodynamics were favorable [17]

From the practical point of view, we would prefer to regard truncus arteriosus Type IV and pseudotruncus arteriosus as separate entities This clear separation does not exist in the literature [7] Stuckey, Bowdler, and Reye[5] in their description of 15 cases of absent sixth arch make no comment on the right ventricular outflow tract and in one of their cases studied pathologically a fibrous strand connected the base of the heart to the left lung a finding incompatible with absence of the sixth arch, the pulmonary blood supply was derived from the descending aorta

Macartney, Deverall and Scott[8] studied the hemodynamic characteristics of the systemic arterial supply to the lungs in 10 cases of absent sixth arch (synonym, truncus arteriosus Type IV) and emphasized the frequent presence of intrahilar stenosis in these vessels Selective injections were performed and the diagnosis made when it was not possible to identify a patent ductus arteriosus or the pulmonary arteries proximal to the hila These authors make the point that the diagnosis of the condition should be made on the nature of the blood supply to the lungs alone and not upon the degree of infundibular atresia It is noteworthy, however, that in six of their ten cases a blind right ventricular outflow tract was present. These findings are at variance with ours where a high degree of correlation between the presence of an infundibulum and the pulmonary arteries was present In only two of our 40 cases with an infundibular chamber were remnants of the sixth arch not identified by angiography

We recognize clearly that there are cases of pseudotruncus arteriosus where the infundibulum is so hypoplastic that angiographic recognition is impossible yet the sixth arch is present fortunately these cases are rare [10,11] Our

study confirms that the two structures frequently co exist and on embryologic grounds the recognition of a right ventricular infundibulum should exclude the diagnosis of truncus arteriosus Type IV as the underlying malformation Such cases should be regarded as examples of pseudotruncus arteriosus with extensive underdevelopment of the sixth arch and extensive aortic collateral supply These variations in the development of the sixth arch have been demonstrated in our study to range from absence of both pulmonary arteries (rarely) one pulmonary artery or segmental divisions of the pulmonary artery to completely normal and confluent pulmonary arteries (Table I)

When an infundibulum is identified, the condition is likely to be pseudotruncus arteriosus with a sixth arch present and the entity is essentially a modality of tetralogy of Fallot with a good potential for surgical correction In the absence of an identifiable infundibulum the malformation is probably truncus arteriosus Type IV (Absent sixth arch solitary aorta with absence of the pulmonary artery and its branches)[9] where the chances of finding collateral vessels anatomically and hemodynamically suitable for surgical correction are very much less

Difference of opinion exists as to whether the aortic collateral vessels are true bronchial arteries or not the suggestion has been made that the large type of collateral vessels represent presistence of the primitive intersegmental branches of the dorsal aortas which supply the lung bud.[15] Further embryologic study is required to clarify this feature Certainly we would agree that when these large vessels are present the pulmonary arteries are usually absent The smaller tortuous type tends to be associated with sixth arch development, suggesting a later development to supply a hypoplastic portion of the sixth arch or the entire arch when there has been closure of the ductus arteriosus they also have the favorable feature that they are often stenotic and protect the pulmonary arteries from high pressure This type of communication has been demonstrated and is known to occur in chronic lung disease[18] The demonstration of these vessels is extremely important since they may be the sole source of blood supply to portions of or the complete sixth arch Adequate demonstration of the anatomy under these circumstances is, therefore best demonstrated by selective catheterization of these collateral vessels rather than by aortography[19]

Summary

The arterial supply to the lungs was assessed in a group of 44 patients with pseudotruncus arteriosus and truncus arteriosus Type IV with a view to surgical correction using a homograft conduit and closure of the ventricular septal defect Biplane right ventricular angiography was performed in all patients and selective catheterization of the collateral vessels was performed in 24 patients above the age of five years In those patients where a blind right ventricular infundibulum was identified (pseudotruncus arteriosus pulmonary atresia and ventricular septal defect) there were 38 patients in whom elements of the pulmonary arteries were identified in 95 per cent and 76 per cent of the patients had anatomy suitable for complete surgical repair In the group where a right ventricular infundibulum was absent (truncus arteriosus Type IV absent sixth arch and solitary aortic trunk with absent pulmonary arteries) there were four patients in whom the sole blood supply to the lungs was derived from aortic collateral vessels and all of the cases were inoperable The collateral circulation to the lungs is described in both groups and the value of selective catheterization of these vessels is stressed The diagnostic value of angiographic identification of the right ventricular infundibulum is emphasized as a pointer to potentially operable cases among a group of patients who have similar clinical features

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Serum enzymes after cardiac surgery under profound hypothermia with circulatory arrest and limited cardiopulmonary bypass

J M Neutze M.D F.R.A.C.P
M J Drakeley M.R.C.S L.R.C.P F.R.C.S
B G Barratt Boyes, K.B.E Ch.M., F.R.A.C.S
Auckland, New Zealand

High levels of serum glutamic oxaloacetic transaminase (SGOT) lactic dehydrogenase (LDH) and creatine phosphokinase (CPK) have been found consistently after cardiac surgery with cardiopulmonary bypass In a study from this Unit, exceptionally high levels were attributed to myocardial damage at operation but baseline elevation of enzymes occurred in all patients subjected to cardiopulmonary bypass[1] Postoperative enzyme levels are now reported in a group of 15 infants who underwent cardiac surgery with profound hypothermia circulatory arrest and limited cardiopulmonary bypass

Methods

The 15 infants were aged 6 weeks to 19 months and weighed 3 to 9 8 kilograms Clinical and surgical details are shown in Table I One patient had recurrent supraventricular arrhythmias and died unexpectedly 10 days after operation Surgical techniques have been described previously[2] Anesthesia was induced with nitrous oxide halothane and oxygen and surface cooling was carried out with a water blanket and ice bags After heparinization connection was made with the infant perfusion circuit and in cyanotic infants cooling was completed with a short period of perfusion Blood was drained from the infant into the machine and intracardiac repair carried out with the heart arrested. Rewarming was achieved rapidly by perfusion

From the Cardiology and Cardiothoracic Surgery Departments, Green Lane Hospital, Auckland, New Zealand.

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Reprint requests to Dr J M Neutze Cardiology Department, Green Lane Hospital, Green Lane West, Auckland, 3 New Zealand.

Total cardiopulmonary bypass time varied from 19 to 48 minutes (average 35 minutes) and arrest time varied from 31 to 79 minutes (average 48 minutes) Postoperatively 12 patients required respiratory support. Where possible assistance was provided by constant positive airway pressure (CPAP)[3] with the infant breathing spontaneously but three patients required an initial period of intermittent positive pressure breathing (IPPB) Twelve patients required infusions of isoprenaline (average maximum dose 0 16 micrograms per kilogram per minute) for suspected low cardiac output infusions being continued for approximately 24 hours in five cases and 48 hours in seven cases Six patients required epicardial pacing early in the postoperative course.

Thirteen lead electrocardiograms were recorded in all patients preoperatively and on the first three postoperative days with at least one further tracing later in the postoperative course Serum SGOT LDH LDH isoenzymes, CPK, and alkaline phosphatase (AP) were measured in nine patients preoperatively and in all patients on the first three postoperative days. Criteria for the electrocardiographic assessment of myocardial damage and methods used for enzyme measurements are described elsewhere[1]

Results

Preoperative and peak postoperative enzyme values are shown in Figs. 1 and 2 Serum levels of AP fell after operation but levels of SGOT LDH, and CPK rose markedly Correlation between postoperative levels of the different enzymes was relatively weak for SGOT LDH R = 0 4996 for

Table I Clinical and surgical details

No	Age (months)	Diagnosis	Arrest temp (deg C)	Arrest time (min.)	Respiratory support	Maximum dose isoprenaline (mcg/Kg/min)	Peak SGOT	Peak LDH	Follow up months	
1	0 5	VSD * Co	21	34	IPPB	0 13	204	390	1	Satisfactory
2	2	ASD APVC	22	34	CPAP	0 14	154	200	3	Satisfactory
3	3	VSD PDA	20	31	IPPB		269	380	1	Satisfactory
4	3	VSD ASD	18 5	40		0 09	272	254	2	Satisfactory
5	5	VSD ASD	21	37			194	320	1	Satisfactory
6	6	VSD	21	55	CPAP	0 03	312	480	Died	10 days
7	7	VSD*	22	43	CPAP	0 04		390	6	Satisfactory
8	19	VSD	22	32	CPAP		205	200	7	Satisfactory
9	11	TF	19	38	CPAP	0 07	184	268	1	Satisfactory
10	13	TF	19 5	54	CPAP	0 05	206	330	4	Satisfactory
11	17	TF	20	49		0 05	206	250	7	Satisfactory
12	1 5	TGA	19	58	IPPB	0 53	218	620	4	Satisfactory
13	3	TGA VSD†	18 22	52 42	CPAP	0 53	168	260	2	Satisfactory
14	4	TGA VSD	17 5	72	CPAP	0 10	270	381	1	Satisfactory
15	7	TGA VSD PS	19	79	CPAP	0 07	294	420	8	CHB

APVC anomalous pulmonary venous connection ASD atrial septal defect Co coarctation of the aorta PDA patent ductus arteriosus PS pulmonary stenosis TF tetralogy of Fallot TGA transposition of the great arteries VSD infracristal ventricular septal defect, VSD muscular ventricular septal defect CPAP constant positive airway pressure CHB complete heart block and IPPB intermittent positive pressure breathing
†Baffle repair revised on first postoperative day

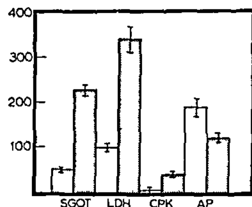


Fig 1 Serum enzyme levels The barographs show the mean values for each group light shading indicating the preoperative level (measured in nine infants) and dark shading the peak postoperative level (measured in 15 infants) Bars indicate ± 1 standard deviation of the mean Units for SGOT LDH and AP are in micromoles per milliliter per minute and for CPK in micromoles per milliliter per hour

SGOT CPK R = 0 5259 no other enzyme pairs showed a significant correlation Individual LDH isoenzymes rose to about the same degree The fraction of total LDH contributed by LDH 1 + LDH 2 (used as an index of myocardial damage) showed no significant change As shown in Fig 3 however, values of LDH 1 and LDH 2 were still rising on Day 3, and although serial changes were not significant it is possible that peak values of these isoenzymes were missed in some cases

There was no electrocardiographic evidence of myocardial damage in any patient Minor coving of ST segments in Cases 12 and 13 was not thought significant and the complete heart block which occurred in Case 15 was related to local surgical trauma

There was no relationship between SGOT, LDH and CPK levels on the one hand, and age weight cardiopulmonary bypass time temperature at arrest or maximal levels of hemolysis on bypass (average 35 mg per 100 ml) Isoprenaline infusion had no detectable effect and there was no relationship between dosage and enzyme levels Neither epicardial pacing nor provision of respiratory support had any apparent effect

There appeared to be some correlation between the duration of arrest time and peak postoperative SGOT levels (Fig 4) but there was considerable scatter and the correlation failed to achieve statistical significance The relationship between arrest time and total LDH levels was similar (R = 0 4764) No LDH isoenzymes showed any closer relationship to arrest time but the cor

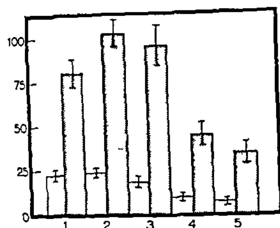


Fig 2 LDH isoenzyme levels in 15 infants Symbols as in Fig 1

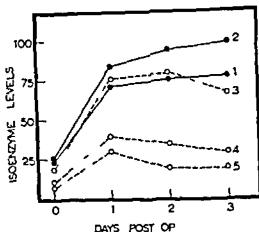


Fig 3 Mean levels of LDH isoenzymes in nine patients preoperatively and 15 patients on the first, second and third postoperative days

relation with LDH 3 and LDH 4 was very similar to that of total LDH

Discussion

Mean preoperative values of the four enzymes were higher in this group of patients who underwent surgery under profound hypothermia than in our group of older patients who underwent surgery on cardiopulmonary bypass [1] and with few exceptions these differences were significant. Peak postoperative SGOT levels were higher in hypothermia patients than in bypass patients with mitral congenital or ischemic disease Peak postoperative LDH levels were higher in hypothermia patients than in all groups of bypass patients including those who underwent aortic or multiple valve replacement Higher levels were seen with each isoenzyme although the differences were most consistent with LDH 2 3 and 4 Although AP levels fell after surgery in hypothermia patients postoperative levels remained higher than those of bypass patients except for the group with congenital disease By contrast differences in CPK levels were not significant

There was no correlation between levels of SGOT LDH and CPK on the one hand and age or weight of the patient, the level of hemolysis the temperature at rest or the duration of cardiopulmonary bypass Observations on arrest temperature and bypass times were however made over a limited range Peak postoperative levels of SGOT and LDH appeared related to the duration of arrest but there was considerable

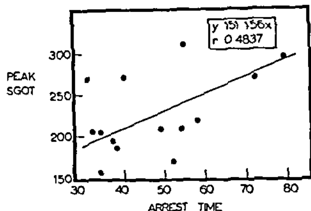


Fig 4 Correlation between arrest time in minutes and peak postoperative SGOT levels in 14 patients

scatter and the correlation was not significant No ready explanation of this scatter was obtained by analysis of the various factors recorded either singly or in combination Ventilation and epicardial pacing appeared to have no influence and no untoward effect was observed from the infusion of isoprenaline up to a dose of 0 5 micrograms per kilogram per minute

Each body tissue has a characteristic pattern of LDH isoenzyme production Heart, kidneys and red cells produce dominantly LDH 1 and 2 thyroid lung adrenal pancreas, and spleen produce greater amounts of LDH 3 the gastrointestinal tract produces greater amounts of LDH 3 and 4 and liver and skeletal muscle produce greater amounts of LDH 4 and 5 The isoenzyme patterns from our patients suggest that LDH was derived from many tissues There was no suggestion of a disproportionate contribution from

Table I Clinical and surgical details

No	Age (months)	Diagnosis	Arrest temp (deg C)	Arrest time (min.)	Respiratory support	Maximum dose isoprenaline (mcg/kg/min.)	Peak SGOT	Peak LDH	Follow up months	
1	0 5	VSD Co	21	34	IPPB	0 13	204	390	1	Satisfactory
2	2	ASD APVC	22	34	CPAP	0 14	154	200	3	Satisfactory
3	3	VSD PDA	20	31	IPPB		269	380	1	Satisfactory
4	3	VSD ASD	18 5	40		0 09	272	254	2	Satisfactory
5	5	VSD ASD	21	37			194	320	1	Satisfactory
6	6	VSD	21	55	CPAP	0 03	312	480	Died	10 days
7	7	VSD	22	43	CPAP	0 04		390	6	Satisfactory
8	19	VSD	22	32	CPAP		205	200	7	Satisfactory
9	11	TF	19	38	CPAP	0 07	184	268	1	Satisfactory
10	13	TF	19 5	54	CPAP	0 05	206	330	4	Satisfactory
11	17	TF	20	49		0 05	206	250	7	Satisfactory
12	1 5	TGA	19	58	IPPB	0 53	218	620	4	Satisfactory
13	3	TGA VSD†	18 22	52 42	CPAP	0 53	168	260	2	Satisfactory
14	4	TGA VSD	17 5	72	CPAP	0 10	270	381	1	Satisfactory
15	7	TGA VSD PS	19	79	CPAP	0 07	294	420	8	CHB

APVC anomalous pulmonary venous connection ASD atrial septal defect Co coarctation of the aorta PDA patent ductus arteriosus PS pulmonary stenosis TF tetralogy of Fallot TGA transposition of the great arteries VSD infracristal ventricular septal defect VSD muscular ventricular septal defect CPAP constant positive airway pressure CHB complete heart block and IPPB intermittent positive pressure breathing
†Baffle repair revised on first postoperative day

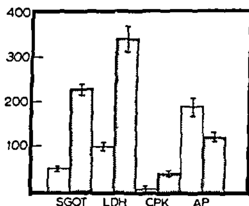


Fig 1 Serum enzyme levels The barographs show the mean values for each group light shading indicating the preoperative level (measured in nine infants) and dark shading the peak postoperative level (measured in 15 infants) Bars indicate ± 1 standard deviation of the mean Units for SGOT LDH and AP are in micromoles per milliliter per minute and for CPK in micromoles per milliliter per hour

SGOT CPK R = 0 5259 no other enzyme pairs showed a significant correlation Individual LDH isoenzymes rose to about the same degree The fraction of total LDH contributed by LDH 1 + LDH 2 (used as an index of myocardial damage) showed no significant change As shown in Fig 3, however values of LDH 1 and LDH 2 were still rising on Day 3 and although serial changes were not significant, it is possible that peak values of these isoenzymes were missed in some cases

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Endocardial fibroelastosis

Etiologic and pathogenetic considerations in children

M J P Schryer M D
P N Karnauchow M D
North Bay Ontario Canada

According to Rossi [101] Lancusi in 1740 was the first to describe endocardial fibroelastosis (EFE) EFE has since been the subject of numerous treatises Its gross and microscopic characteristics are well known but its etiology and pathogenesis are still in a state of utter confusion as reflected in innumerable past and present hypotheses These include mural endocarditis [74 98] myocarditis [2 44 45 54 111 112] anoxia [66] mechanical obstruction of blood outflow (hemodynamic) [11 30] myocardial endocardial and elastic hyperplasias [33, 51 95] aortization of the endocardium [29] collagen disease [65] autoimmunity [116] *hereditary* disorder [89] congenital *metabolic* disease [12 68] lymphatic obstruction [85] and many other single and combined proposals such as maternal toxins [40] and status thymico lymphaticus [23] Some of the above are difficult to understand and one gains the impression that many were the result of a revelation rather than that of fact and logic Furthermore most of the authors based their theories almost exclusively upon their own series and often failed to take advantage of the vast material available in the world literature

Materials and methods

Protocols and sections of 12 autopsies of infants dying of EFE in St Joseph s (AJ) and Civic (AC) Hospitals in North Bay Ontario Canada also ninety four protocols and sections of autopsies from the Hospital for Sick Children Toronto and the Ottawa Civic and General Hospitals Ottawa Ontario Canada constituted the basic material for this study

From th Departments f Pathology North Bay Civi H sp tal, a d St. Joseph s Ge eral Hosp tals N rth B y O ta Canada
Recei ed for publ t on Jan. 23 1974

Case reports

1 AJ 76 10 month-old female admitted with cough and fever Autopsy acute bronchopneumonia edema of lungs and hydrothorax EFE of left ventricle with closed *foramen* ovale and ductus arteriosus No valvular *lesions* *Coronary* arteries normal

2 AJ 622 four month old female admitted with croup of four days duration. Autopsy acute interstitial pneumonia laryngotracheitis and edema of lungs EFE of left ventricle with closed foramen ovale and ductus arteriosus No valvular lesions Coronary arteries normal

3 AJ 702 five week-old male admitted with intermittent cyanosis Coarctation of aorta was suspected Autopsy chronic interstitial pneumonia (diffuse septal fibrosis) EFE of right ventricle and auricle with scars of myocardium postendocarditic scarring of mitral valve leaflets bicuspid aortic valve closed foramen ovale and infantile coarctation of aorta Coronary arteries normal

4 AJ 786 *one* and one *half* hour old male admitted with *gross edema* bradycardia, and cyanosis Pregnancy was complicated by polyhydramnios Autopsy EFE of hypoplastic left *ventricle* with hypoplasia of aorta aortic and mitral valves closed foramen ovale and patent ductus arteriosus

5 AJ 1009 two day-old male premature had vomiting pallor and intermittent periods of "stiffening out Autopsy EFE of *right ventricle with* myocardial scars and hypertrophy and dilation hypoplasia of left *ventricle* atresia of aorta and aortic valve hypoplasia of mitral valve persistent septum primum patent ductus arteriosus and dilation of pulmonary *artery*

6 AJ 1048 two day old male had periodic apnea cyanosis and listlessness Autopsy EFF of right atrium and common ventricle (cor triloculare) with transposition of great vessels atresia of mitral and aortic *valves* and patent foramen ovale and ductus arteriosus

7 AC 209 five month old male hermaphrodite died suddenly Autopsy edema of lungs EFE of left auricle and ventricle with hypertrophy and dilation and closed *foramen ovale* and ductus arteriosus No valvular lesions Coronary arteries normal

8 AC 360 18 month old female *admitted* with dyspnea and cyanosis of three days duration *Autopsy* acute interstitial pneumonia and hydrothorax *EFE of* left ventricle with myocarditis and closed foramen ovale and ductus arteriosus No valvular *lesions* Coronary arteries normal

myocardial tissue, but LDH isoenzymes are less useful in this regard after operation than after myocardial infarction [1] On the other hand, there was no electrocardiographic evidence of myocardial damage to explain the high enzyme levels as there was in patients undergoing surgery with cardiopulmonary bypass

Release of enzymes under conditions of hypothermia and cardiac arrest could be due to a number of factors including tissue hypoxia and acidosis, limitation of substrate availability, or a direct effect on permeability of cell walls The level of acidosis with hypothermia is insignificantly higher than with cardiopulmonary bypass[4] and other factors are probably more important Release of enzymes in animals and humans subjected to hypothermia has been recorded frequently,[5, 6] but conditions have been very different from those to which our patients were subjected Rittenhouse and co workers[7] examined the effects of hypothermia on dogs cooled and rewarmed by surface means with maintenance of a temperature of 18 to 20° C for 30 to 90 minutes Myocardial lesions were found consistently and were more marked in animals in whom potassium arrest was induced Changes in lungs kidneys spleen liver and brain were of doubtful significance At present there is no evidence of tissue damage with the technique used in our patients but systematic experimental studies have not been carried out

Summary

Electrocardiographic and enzyme studies were made on 15 infants undergoing cardiac surgery with profound hypothermia circulatory arrest, and limited cardiopulmonary bypass The following observations were made preoperatively and on the first, second and third postoperative days 13 lead electrocardiograms serum SGOT, LDH LDH isoenzymes, CPK, and AP At least one further electrocardiogram was recorded later in the hospital stay

Serum levels of AP fell after operation but levels of the other enzymes including all LDH isoenzymes rose There was no correlation between enzyme changes and the age or weight of the patient duration of cardiopulmonary bypass, temperature at arrest the level of hemolysis or with postoperative complications, but the correlation with arrest time approached significant levels The pattern of LDH isoenzyme production suggested that many tissues were involved in enzyme release

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by Dewitski[30] and later supported in one form or another by others[6 11 12 14 20 38] emphasized the overstretching of the endocardium and its subsequent thickening either due to obstruction of the outflow tracts or because of weakness of the myocardium itself

This concept finds no confirmation in the cases collected. Indeed, if stenosis of the aortic and mitral orifices is to be considered a causative factor one should have more than a few cases displaying such obstructive lesions[8] Reports of stenoses of various orifices or of coarctation of the aorta without EFE[18 19 91 101] do not lend much credibility to Dewitzki s theory Furthermore if the hemodynamic theory was correct one certainly would not expect to find EFE in the left ventricle in association with an interventricular septal defect[20 21 44 45 53 84 114]

The theories based upon a primary myocardial disorder due to either an enzymatic defect[66] or a hyperplasia[12] resulting in undue stretching of the endocardium likewise cannot be taken too seriously since the involvement of all four chambers in the cases collected thus far represents a minority In addition it seems to us that this theory is based on pure speculation as far as the enzymatic myocardial defect is concerned.[68]

The fact that on occasion endocardial fibroelastosis is associated with such metabolic disorders as von Gierke s disease[32 48 101] and others[27 89] does not necessarily mean that some known or unknown metabolic disorder weakening the myocardium is active in the production of EFE in all instances Indeed Wilson and Clark[1 4] report three cases of glycogenosis one of which failed to show endocardial involvement In the two cases with EFE only the left ventricles were involved Could not the two entities exist side by side fortuitously?

The myocardial hyperplasia advanced by Black Schaffer and Turner[12] has not only failed to be confirmed by others but is in direct contradiction with the findings of Dammin and Moore[28]

The concept of primary (idiopathic) and secondary EFE is not accepted by Moller and coworkers[87] and others[6 11 12 32 44 69 86] and we agree with the former authors' comment that these terms suggest etiological implications that can not be confirmed. Crome[47] suggested that the designation EFE be used to imply a nonspecific structural change rather than a disease entity a most sensible statement considering the state of the problem

Hill and Reilly[55] postulate that EFE is a collagen disease because of the finding of the fibrinoid material within the lesion So far Scarrizza[107] seems to be the only supporter of this contention We have failed to see similar material in our cases and like Adams and Katz[1] we do not feel that such a theory should be seriously entertained.

Hull Binns and Joyce[61] believe that the condition may be due to transplacental transmission of unspecified antibodies (i.e infant s mother had lupus erythematosus) Kugel[75] states that the cardiac changes may represent the result of an allergic response to infection probably of a viral type Donat[34] speaks of the possible sensitization of endocardial endothelium which reacts to a subsequent infection of a minor nature with resulting development of EFE Loew Lowenthal and Keusch[80] believe that the allergic reaction alone or combined with an infection may be responsible for such changes Although the possibility of such speculations cannot be completely ignored nevertheless the absence of concomitant lesions of a similar type in the endothelial or other mesenchymal components elsewhere seems to greatly reduce the value of such proposals

The theory of spontaneous abnormal proliferation of embryonal endocardium[33 37 69 96] or overgrowth of the bulbus cordis into the endocardium[25] is not supported by the tabulated material The table indicates that a considerable number of hearts had atrial involvement, some exclusively[53 83 114 119] in many instances the right ventricle was involved not only together with the left[12 26 31 44 53 65 69 77 84] but also independently[12 29 41 53 56 84 101]

Many authors contend that EFE is a congenital developmental malformation because of the frequency with which it was associated with other cardiac malformations[21 47 56 57 127 129] Some consider the disease as hereditary[34 81] on the basis of its occurrence in consecutive siblings

There is little evidence to support the latter on such a basis since the overwhelming majority of the reported instances occurred in individual siblings It is also believed that the disease is secondary to some agent or is associated with maternal disease[61] To support this one may refer to Forrester Lees and Watson[42] who reported the

Table I

Total cases (Children up to 10 years)		World review (729)	Ontario cases (106)
Left side only		576	94
Right side only		35	5
Both ventricles		76	6
All chambers		42	1
Foramen ovale	Patent	124	43
	Closed	158	42
Ductus arteriosus	Patent	129	44
	Closed	139	51
Anomalous lt coronary artery		25	2
Aortic	Stenosis	116	35
	Insufficiency	6	0
Mitral	Stenosis	101	19
	Insufficiency	13	3
Coarctation of aorta		31	20
Interventricular defect		12	5
Myocarditis		137	5
Myocardial scars		215	14
Myocardial calcification		12	3

9 AC 689 48 hour old male with cyanosis and signs of cardiac failure Autopsy EFE of left ventricle with hypoplasia stenosis of aortic and mitral orifices and patent foramen ovale and ductus arteriosus

10 AC 837 six week old male admitted with failure to thrive vomiting and cyanosis Autopsy EFE of left ventricle with myocardial scars and hypertrophy postendocarditic scarring of mitral and aortic valves stenosis of aortic orifice patent foramen ovale and closed ductus arteriosus

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12 AC 944 seven month old female admitted with grunting respiration irritability anorexia and vomiting of one month duration Autopsy EFE of right auricle with nonfusion of septum secundum postendocarditic scarring of tricuspid valve insufficiency of tricuspid orifice hypertrophy of right ventricle and closed ductus arteriosus Coronary arteries normal

In all cases, gross and microscopic features were recorded and arranged in groups according to the site or sites of lesions, the state of the foramen ovale, ductus arteriosus, coronary arteries, aortic and mitral valves, presence of coarctation of the aorta intraventricular septal defect, myocarditis, myocardial scars and myocardial calcification

In addition, 729 cases were selected from the literature mainly on the basis of statements concerning the above listed gross cardiac lesions Histologic lesions, whenever described in the same cases, were collected and arranged in groups as well

Results

The collected data from the Ontario group of cases as well as that from the cases published in the medical literature is tabulated in Table I This shows that, although in the vast majority of cases EFE occurred on the left side of the heart, it is encountered on the right side as well In some instances, both ventricles alone are affected and in others all chambers of the heart are involved In about one fifth of the cases from the literature and in a third of the Ontario cases, the foramen ovale was found to be open The findings were similar in the cases of aortic stenosis. In 17 cases there was a deficient interventricular septum Myocarditis and myocardial scars and calcifications were found in a fifth of Ontario cases and in about half the cases collected from the literature

In the vast majority of cases studied there was no evidence either clinical or morphological of metabolic disorders or collagen diseases The incidence of EFE in siblings was negligible The maternal history in most of the cases in both groups was either negative or not available

Discussion

The anoxic theory proposed by Johnson and supported by a number of authors[59 82] implies impediment of oxygenation of the endocardium and myocardium due to such abnormalities as anomalous origin of the left coronary artery, congenital absence of the left coronary artery congenital stenotic and atretic lesions of valvular orifices and premature closure of the foremen ovale

A glance at the table would show that this theory does not apply to the majority of cases of EFE since EFE was present in hearts with patent foramen ovale and absent in the instances where even both coronary arteries arose from the pulmonary artery[3 113]

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The hemodynamic theory originally proposed

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The hemodynamic theory originally proposed



Fig 4 (ACH 522) *Diffuse sclerosis of myocardium in a case of* well established endocardial fibroelastosis HPS ×100



Fig 5 (ACH 191) Focal myocarditis in a case of viral pneumonia HPS ×100

has been confirmed by our series (cases 2 3 and 8) showing a variety of lesions spanning from acute myocarditis to myocardial scars (Figs 1 2 3 4 and 6) The postulation of the so called serous myocarditis or inflammatory edema[2, 102] without cellular exudate does not seem to be either necessary or reasonable How does one distinguish simple edema from so called serous myocarditis or lymphedema? The latter possibility was nevertheless raised recently by Miller Pick and Katz.[85]

According to Easterly and Oppenheimer[36] the endocardial changes were related to myocardial scarring in nearly two thirds (62 per cent) of the *specimens with associated cardiac malformations* Fruhling and co workers[45] state that one should almost constantly find either inflammatory lesions *or scars in the affected hearts provided* that more than a single section of myocardium is examined House[59] found thickening of the endocardium *in cases of viral myocarditis while* Hübschmann[60] reports similar findings in cases associated with myocarditis of diphtheria The finding of *focal calcifications of the myocardium* in many cases[38 6 71 103 106 114 116 125] strongly suggests antecedent destructive lesions The occurrence *of such* a spectrum of myocardial involvement indicates that there is more than an incidental relationship between inflammatory lesions *of the myocardium* and EFE In our case No 12 involvement of the right auricle with concomitant scarring of the tricuspid valve could *only be explained on the* basis of inflammation i.e localized myocarditis and endocarditis. Similarly the involvement of the right ventricle cases 3 5 and 11 *must have* been caused by an



Fig 6 (ACH 702) Focal myocardial sclerosis in a case of well established endocardial fibroelastosis HPS ×100

inflammatory lesion since morphologic evidence *of all other causative factors* thus far postulated are absent. Moreover the myocardium in the third and fifth cases showed scattered patchy *scars*

In those instances where scars of the myocardium were not observed[21 57 94 97 98 99 122 123] one *may also* suggest that they *were obliterated* by compression and stretching of the myocardium during its subsequent growth In a similar vein Loew Lowenthal and Keusch[80] state that the defective septa due to maternal rubella do not show evidence of inflammation it is therefore possible that congenital vitia can be caused by infection which does not leave any trace of an inflammation of either the endocardium or myocardium

The instances of twins or triplets[95 98 119] where only one of the siblings suffered the disease were used by some authors[57 111] as an argument



Fig 1 (ACH 360) Diffuse myocarditis with early endocardial fibroelastosis HPS ×100



Fig 3 (ACH 360) Proliferation of elastic fibers between degenerating myocytes in the subendocardial myocardium Verhoeff's stain ×400



Fig 2 (ACH 360) Fibrous thickening of endocardium with intermixed elastic fibers Verhoeff's stain ×100

escape of a binovular twin in rubella syndrome Only one of the twins was malformed but both had identical rubella neutralizing antibody titers of 1 256 Indeed the modern thinking concerning congenital cardiac malformations is based upon the implication of viral infection [15 16]

Although we agree in general that the disease could be considered a malformation since most of the cases were developed in utero however, leaving it at that without further attempt at clarification of its etiology does not seem reasonable Furthermore EFE developing after birth surely cannot be considered a malformation

Recently Miller Pick, and Katz[85] and Kline and co workers[72] reported the production of EFE by ligation of cardiac lymphatics in dogs and postulate this as a possible pathogenetic pathway Nevertheless, Miller, Pick, and Katz[85] suggest that the cardiac lymphatic obstruction may be secondary to chronic myocarditis

The theory that EFE is secondary to an inflammatory disease of the heart is the oldest one and is perhaps the least popular on this continent. Kreysig[74] coined the term "mural fetal endocarditis" and believed it to be due to *Mycobacterium tuberculosis* though others implicated *Treponema pallidum*, *Diphtheria* [60] etc The authors[80 89] who rejected the inflammatory theory were in fact, rejecting this concept of 'fetal endocarditis' and we believe they were right in doing so

The concept of EFE as an aftermath of myocarditis was recently proposed by a number of authors[59 60] but was again rejected because of the lack of definite acceptable morphologic evidence of inflammation [51 100]

However, the hurdle that Rosahn[100] refers to, appears to have been overcome by several authors notably Fruhling and Adam [44] Afanas eva Ivanovskaya and Zhukova[2], Freundlich and co workers [43] Stober [111 112] Hariga,[54] Orshanskaya [93] Gjertsen [46] Kenny and Sanes [70] and others [118 120 126] Stöber[111 112] and Fruhling and co workers [45] noticed the increased frequency of deaths due to EFE following epidemics of viral disease and Case[22] noted a seasonal incidence Noren Adams and Anderson[90] suggested the possibility of intrauterine infection with mumps as a cause of EFE Fruhling and co workers[45] have seen EFE in association with acute pancarditis and acute and chronic myocarditis, and consider the frequently found myocardial scarring as the result of the latter [8 10] Recently Hutchins and Vie[64] showed histologic evidence of progression of myocarditis to EFE This

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against the infective theory However, one should not expect all siblings in a multiple pregnancy with multiple placentas to be necessarily affected [33,42,5,115] It is also not necessary to have a viral disease in the mother herself [86] Indeed, Mitchell and co workers[86] in their epidemiologic assessment of EFE failed to demonstrate any consistent association between viral infection in the mother and "primary" EFE in the offspring

Thus it seems reasonable to think that in most instances EFE can be considered an aftermath of inflammation of the myocardium in spite of the fact that not all cases of myocarditis will lead to EFE [88,9,101] Perhaps the extent of the myocardial involvement is an important factor in the production of EFE as well as its severity Also the absence of EFE in some instances of acute myocarditis may possibly be explained by the short interval between onset and death precluding the development of EFE [9] The proliferation of endocardial elastic fibers is most likely caused by some product of myocardial degeneration but not necessarily by a product of viral metabolism alone [78,109] After all on occasion evidence of EFE is observed in areas of myocardial infarctions in adults where there is no reason to suspect a viral infection The possibility of a pathogenetic role by hemodynamic forces promoting the proliferation of elastic fibers in the presence of a weakened myocardium[104] cannot be completely denied on the basis of present knowledge [63]

Fruhling and co workers[45] Stöber[111,112] as well as Hariga[54] and Freundlich and co workers[43] suggest that the disease is caused by a virus though studies of maternal and children s serum antibodies to viruses such as mumps and Coxsackie were rather disappointing [86,90,105] However only a few authors have investigated the cardiotropic viruses to date [66] Thus far the fluorescent antibody technique has not been used but may be an important procedure in elucidating the problem

The theory of a viral etiology and of a pathogenetic progression from myocarditis to scarring and elastosis appears to be indeed the only one that can explain the occurrences of EFE in all chambers of the heart, or in any of the various combinations thus far observed, including those associated with other cardiac malformations In order to finally resolve this problem we suggest that in the future fresh autopsy and biopsy material be examined by fluorescent antibody techniques, the epidemiology of each case carefully studied and sera of both the child and the mother be examined for antibodies to all viruses known to have a cardiotropic propensity

Summary

Extensive and detailed review of the World literature pertinent to the problem of EFE and the study of 106 cases from several hospitals in Ontario, Canada, indicates that the disease is most probably of a viral etiology and is a sequel to myocarditis or pancarditis Such a pathogenetic pathway seems to be the only one that can explain the morphologic variations of the disease and its concomitant cardiac lesions

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pressure determinations left ventricular cineangiography and oximetry Indicator dilution dye curves were done when indicated Left ventricular cineangiograms were done in the left anterior oblique (LAO) position using Renografin 76

Of the 44 patients 22 were males and 22 were females The average age at the initial catheterization was ten (range seven months to 55 years) A total of six patients (Group A plus one patient not having a follow up examination) were found to have a ventricular septal aneurysm without a ventricular septal defect at the time of their initial catheterization In each instance the patient was catheterized for an unrelated lesion and the aneurysm was an unexpected finding None of these patients had a holosystolic murmur described on previous examinations or heard on our follow up study

Follow up examination was possible in 36 patients In this group there were 27 patients that had a previously documented open ventricular septal defect with a ventricular septal aneurysm None of these patients had an associated lesion which would obscure a decrease in the intensity or duration of the ventricular septal defect murmur Three patients had a significant decrease in the intensity and duration of the murmur Two refused catheterization and the third had an open ventricular septal defect as demonstrated by indicator dye dilution curve with injection of dye into the left ventricle and sampling in the main pulmonary artery Six other patients were re catheterized after an average follow up period of seven years and two months All were demonstrated to have a patent ventricular septal defect (Table II)

The average follow up period for the 27 patients with open and uncomplicated defects was four years and ten months (range 18 months to 15 years) There were no left to right shunt ratios larger than 1 5 1 and the majority of patients had shunts too small to calculate by oximetry Four patients had associated mild aortic insufficiency Echocardiograms and electrocardiograms were normal in these uncomplicated cases

Discussion

Spontaneous closure of membranous ventricular septal defects has been well documented[27] However except for adherence of the septal leaflet of the tricuspid valve to the margins of the defect[28] the mechanism of closure in the majority of cases remains obscure The association of ventricular septal aneurysms with ventricular septal defects has led to speculation concerning the role the aneurysm might play in spontaneous closure of the defect

Edelstein and Charms[20] suggested that such a combination resulted from an attempt at closure of the defect with aneurysm formation secondary to a high left to right ventricular pressure gradient Jain and Rosenthal[1] questioned whether these aneurysms were a late manifestation or an early accompaniment of a ventricular septal defect Varghese and Rowe[23] postulated that defect closure and aneurysm formation were secondary to the same process namely endocardial proliferation or hypertrophy on the right ventricular side of the defect Misra and co workers[24] demonstrated late aneurysm formation with reduction in shunt size in three patients and postulated that the formation of an aneurysm was a prelude to closure as well as a mechanism of closure

The shunt size of ventricular septal defects with associated aneurysm has been almost exclusively small[2-29] Varghese and co workers[22] reported 16 cases of septal aneurysm in 48 patients with ventricular septal defects Of those with aneurysms 88 per cent had pulmonary to systemic flow ratios of 1 4 to 1 or less No aneurysms were found in patients with flow ratios greater than 2 2 to 1 Our data is in agreement with these findings since no patient had a flow ratio greater than 1 5 to 1

In our initial groups of 44 patients there were six patients who had an aneurysm without a ventricular septal defect confirmed by cathe

Table I Study groups

	Follow up	No follow up	Total
Group A*	5	1	6
Group B†	4	0	4
Group C‡	27	7	34
Total	36	8	44

*Ventricular septal aneurysm and no ventricular septal defect
†Ventricular septal aneurysm and patent ventricular septal defect plus other significant complicating congenital lesions
‡Ventricular septal aneurysm and patent ventricular septal defect without other significant congenital cardiac lesions

Natural history of ventricular-septal defects associated with ventricular-septal aneurysms

Mark E Lambert, M D *
Steven Widlansky, M D *
Edmund A Franken, M D
Roger Hurwitz M D, F A C C
Richard Nielson, M D
William K Nasser M D, F A C C
Indianapolis, Ind.

Since Laennec's original description of an aneurysm of the membranous ventricular septum, numerous other case reports and reviews have appeared in the literature[2-9] Steinberg[10] was the first to demonstrate a septal aneurysm by angiography and subsequently, other reports followed[11-13] These aneurysms of the membranous portion of the interventricular septum have been associated with various congenital lesions[3,4,7,11,14,15] the most common being a ventricular septal defect[7,16-19]

Various authors have commented upon the possible association of certain of these aneurysms with spontaneous closure of a ventricular septal defect[20,21] Furthermore Varghese and co workers[22,23] and Misra and co workers[24] have, in fact, raised the question as to whether the appearance of such an aneurysm is a prelude to spontaneous closure of the ventricular septal defect

In view of the frequency of ventricular septal defects[25] and the uncertainty involving their natural history[25,26] *the value of being able to predict spontaneous closure is obvious Thus, a study was undertaken to determine the natural history of ventricular septal defects associated with septal aneurysms*

Methods

The left ventricular cineangiograms and cardiac catheterization data of all ventricular septal defects and/or aneurysms of the ventricular septum were reviewed by three observers There were more than 250 studies examined and 44 patients with an aneurysm of the ventricular septum were found

Thirty six (36) patients having adequate follow up examinations were divided into three groups (Table I) Group A patients had a ventricular septal aneurysm and no ventricular septal defect Group B patients had a significant congenital cardiac anomaly in addition to a ventricular septal aneurysm and a patent ventricular septal defect Group C patients had a ventricular septal aneurysm and a patent ventricular septal defect without significant additional complicating cardiac lesions There were 5 4 and 27 patients in Groups A, B, and C, respectively

The follow up examination consisted of a history physical examination electrocardiogram phonocardiogram, and echocardiogram Indications for repeat cardiac catheterization were a decrease in the previously described murmur by two grades (out of six), shortening of the murmur (if previously holosystolic), and necessity for hemodynamic re evaluation as judged by the primary care cardiologist

Seven patients in Group C had repeat cardiac catheterization (Table II) All studies included

From the Krannert Institute of Cardiology Marion County General Hospital and the Department of Medicine Pediatrics and Radiology Indiana University School of Medicine Indianapolis

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Reprint requests to Dr Steven Widlansky 1100 W Michigan St Indianapolis Ind. 46202

United States Public Health Service Trainees in cardiology

We feel that despite the presence of an aneurysm if the ventricular septal defect remains open past the first few years of life it is unlikely to close completely

Summary

The diagnosis of ventricular septal aneurysm was established by left ventricular cineangiography in forty four patients Six of the patients had a ventricular septal aneurysm without a ventricular septal defect at the time of their initial catheterization Twenty seven patients who had a ventricular septal defect and ventricular aneurysm as their only significant cardiovascular lesion were followed for a mean of four years and ten months The left to right shunt ratio was less than 1 5 1 in all cases Shunt size decreased in six out of seven patients subjected to repeat catheterization In no case were we able to document complete closure of the ventricular septal defect Thus although a ventricular septal aneurysm may represent a mechanism for partial closure of a ventricular septal defect, complete closure of the defect appears unlikely if it remains open past the first few years of life

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Table II Catheterization data

Patient	Sex	Age at initial catheterization	L R shunt* (%)	Cine	MPA (mm. Hg)	Age at repeat catheterization	L R shunt* (%)	Repeat cine	MPA (mm. Hg)
J A	F	14 mos	43	VSA + VSD	45/18	7 yrs	17	VSA + VSD	17/5
M C	M	7 mos	33	VSA + VSD	35/15	7 yrs	N.S	VSA + VSD	22/7
B I	F	29 yrs	N S	VSA + VSD	17/4	36 yrs	N S	VSA + VSD	26/5
C K	F	13 yrs	27	VSA + VSD	25/9	22 yrs	N.S	VSA + VSD	23/8
S P	F	8 yrs	28	VSA + VSD	23/9	13 yrs	N S	VSA + VSD	27/7
R P	M	2 yrs.	33	VSA + VSD	41/15	6 yrs.	N.S	VSA + VSD	31/12
J S	M	5 yrs	33	VSA + VSD	22/4	15 yrs	22	VSA + VSD	26/6

Calculated using oxygen saturation
Cine = Left ventricular cineangiograms in left anterior oblique projection mos = months MPA = main pulmonary artery pressure in mm Hg
VSA = ventricular septal aneurysm VSD = ventricular septal defect N.S = not significant and yrs. = years.

terization No diagnosis of ventricular septal defect was ever recorded in any of these six patients Therefore we feel these patients lend no support to the concept that ventricular septal aneurysms are a prelude to the late spontaneous closure of ventricular septal defects On the other hand we cannot rule out the possibility that these patients were merely studied late in the course of their ventricular septal defects

Varghese and Rowe[23] have presented the only patient in whom initial cardiac catheterization revealed a patent ventricular septal defect with an associated aneurysm and subsequent catheterization showed a residual aneurysm with complete closure of the ventricular septal defect The three cases reported by Misra and co workers[24] all had a decrease in the size of their shunts at a second catheterization but the defect had not closed in any of their patients

There were 27 patients in our study who had a proved ventricular septal defect with an associated ventricular septal aneurysm These patients were considered separate from the original groups of 36 patients that had follow up examinations because they had no other cardiovascular lesions which would obscure the typical holosystolic murmur of the ventricular septal defect In this age group there were only three patients who had a decrease in their murmurs when compared to their initial examination The one patient that agreed to re catheterization had an open ventricular septal defect (Table I *C K*) If we assume that the remaining two patients had closed defects we have a closure rate of 7 4 per cent over a period approaching five years

Seven patients had repeated catheterizations (Table II) The average interval between catheterizations was seven years and two months In all but one patient (B I) there was a decrease in the left to right shunt as determined by oximetry We are unable to determine how much of the decrease is due to growth factors per se as opposed to a decrease in the size of the defect Significantly, there was not one example of closure of a ventricular septal defect

We agree with Edelstein and Charms[20] and Varghese and co workers[21,23] that the ventricular septal aneurysm most likely occurs secondary to attempted closure However our data does not support the concept of spontaneous closure

Table I Clinical features of six patients with *Pseudomonas* endocarditis

Patient	*Fever*	*Murmur*	*Splenomegaly*	*Splinter hemorrhages*	*Clubbing*	*Skin stigmata of intravenous drug abuse*	*Pleural rub*	*Hematuria*	*Initial WBC*	*Radiological evidence of cavitating infiltrates*
1	+	+	+	+	–	+	–	+	17 400 left shift	–
2	+	+	+	–	–	+	+	–	14 000 left shift	+
3	+	+	+	–	–	+	+	–	9 400 normal differential	+
4	+	+	+	–	+	+	–	–	9 800 normal differential	+
5	+	+	+	–	+	+	–	–	7 200 left shift	–
6	+	+	–	–	–	+	+	+	10 200 left shift	+
Total	6/6	6/6	5/6	1/6	2/6	6/6	3/6	2/6	2/6 high	4/6

Table II Blood cultures in six patients with *Pseudomonas* endocarditis

Patient	*Organisms at admission*	*No cultures positive*
1	*P aeruginosa*	6/8 on Day 1 (Pseudo) 4/4 over next 2 weeks (Pseudo)
2	*P aeruginosa*	6/6 on Day 1 (Pseudo) All negative during therapy 2/13 after therapy before discharge (Pseudo)
3	Group A beta hemolytic *streptococcus*	4/4 on Day 1 (Gr A Strep) 8/8 on Day 5 (Pseudo) All positive until surgery (Pseudo) Negative afterwards
4	*S fecalis*	4/4 on Day 1 (*S fecalis*) 1/4 on Day 13 (Pseudo) All positive over next 8 months (Pseudo)
5	*P aeruginosa* and *S viridans*	4/4 on Day 1 (Pseudo and *S viridans*) 5/5 on Day 12 (Pseudo) Negative for 3 months with relapse (Pseudo)
6	*S aureus* and *P aeruginosa*	6/6 Day 1 (*S aureus* and Pseudo)

H p tal day when pos t blood cultur w re dr wn.

docarditis was not initially suspected as the source of bacteremia In only one patient was *Pseudomonas* the first and only organism isolated from blood cultures Four patients had other organisms grown from blood culture on admission to the hospital and *Pseudomonas* was eventually recovered and persisted after the initially recognized pathogens were treated successfully (Table II)

Antibiotic therapy Five out of six patients were treated with gentamicin for practically their entire course of medical therapy The mean duration of therapy in these five patients was 94 4 days (range 36 to 171 days) The usual dosage was 4 5 mg per kilogram per day in divided doses in patients with normal renal function There was no good evidence of ototoxicity or renal toxicity from gentamicin in any of the patients All five patients also received carbenicillin for most of the course of treatment in addition to gentamicin The usual dosage of carbenicillin was 30 to 40 Gm per day Two patients received

Pseudomonas aeruginosa endocarditis in drug addicts

Gordon Archer, M D
F Robert Fekety M D
Ronald Supena M D
Ann Arbor and Eloise Mich.

Bacterial endocarditis is a serious medical complication of heroin addiction and should be suspected in any addict with a fever and positive blood cultures However gram negative bacteria and particularly *Pseudomonas aeruginosa* are uncommon causes of bacterial endocarditis and their presence in a blood culture may be dismissed as a contaminant or as originating from another site Therefore to call attention to the problem and its clinical features we are reporting six recently observed cases of *P aeruginosa* endocarditis in heroin addicts

Materials and methods

All patients were seen at one of the University of Michigan Affiliated Hospitals between Nov 1970 and April 1972 The criteria for the diagnosis of *Pseudomonas* endocarditis were (1) multiple blood cultures positive for the organism (2) absence of another source of bacteremia, and (3) either a significant cardiac murmur or a specimen of the valve which harbored the organism as determined by culture or microscopic examination *P aeruginosa* was identified from blood cultures using standard laboratory procedures[1] In vitro antibiotic susceptibility studies were performed with standard Kirby Bauer disc techniques using a 50 microgram carbenicillin disc[2] Serial broth dilution susceptibility studies were performed in Mueller Hinton broth using a microtiter plate method[3]

General characteristics All of the patients were heroin addicts There were five men and one woman The mean age was 35 7 years and all were black

Clinical features The duration of symptoms before the onset of therapy varied from several days to six months All of the patients were febrile, and five of the six had splenomegaly In five patients, the infection involved the right side of the heart, the sixth patient having endocarditis of a prosthetic aortic valve Four of the infections involved previously normal valves and two were on prosthetic valves Four of the five patients with tricuspid valve endocarditis had pulmonary emboli All four patients were symptomatic with chest pain and shortness of breath and three had audible pleural rubs A murmur referable to the involved valve was heard in every instance but in two patients a faint systolic murmur suggestive of tricuspid insufficiency was appreciated only in restrospect after the diagnosis had been firmly established Evidence of peripheral emboli such as petechiae splinter hemorrhages Roth spots and hematuria was found in only two of the six cases (Table I) One of the two was a patient with aortic valve involvement, and the other had concomitant bacteremia with *Staphylococcus aureus* Three patients remained remarkably well clinically during several months of continued *Pseudomonas* bacteremia None of the patients developed hypotension during their *Pseudomonas* sepsis Two patients were found to be using intravenous drugs while in the hospital and in two others this was suspected.

Results

Blood cultures Multiple blood cultures were positive in all cases but in three instances en

From the Department of Internal Medicine Section of Infectious Diseases University of Michigan Medical Center Ann Arbor and the Wayne County General Hospital Eloise Mich

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Reprint requests to Dr Gordon Archer Veterans Administration Hospital Ann Arbor Mich 48105

Table IV Pathologic findings on valves at surgery or autopsy in six patients with *Pseudomonas* endocarditis

Patient	*Valve involved*	*Gross*	*Microscopic*	*Culture*
1	Prosthetic aortic	Vegetations on struts	Gram positive cocci	*S. fecalis*
2	Tricuspid	No specimen	No specimen	No specimen
3	Tricuspid	Valve friable and thickened	Chronic inflammation No organisms seen	Valve negative but left atrial blood culture positive for *P aeruginosa*
4	Tricuspid	Leaflets sclerotic and thickened with firm vegetations	Covered with fibrinous exudate No organisms seen	*P aeruginosa*
5	Prosthetic tricuspid	Vegetations on struts	Not done	*P aeruginosa*
6	Tricuspid	Acute valvulitis	Necrotizing arteritis and myocarditis gram negative rods	Not done

cultures remained negative after surgery in the latter two patients who were continued on anti biotics. These two patients were free from infec tion had minimal signs of congestive heart failure and had returned to work when seen three months postoperatively They have been lost to follow up since that time

The mean duration of hospitalization was 3 8 months with the shortest seven days and the longest eight months None of the three patients who survived has returned for more than one out patient follow up visit

Pathologic data There were five patients from whom tissue from the involved valve was ob tained for examination (Table IV) *P aeruginosa* was cultured from two patients and gram nega tive rods were seen in the valve of a third patient whose postmortem heart blood culture grew the organism A fourth patient presumably had his valve sterilized of *Pseudomonas* by antibiotic therapy and died of endocarditis due to *S fecalis* A fifth patient ceased having positive blood cul tures after the removal of a chronically inflamed valve although the section of valve cultured was sterile

Illustrative cases

Patient No 1 a 29 year old male was a known heroin addict who was admitted to the Wayne County General Hospital on Oct. 30 1971 A di agnosis of acute *Staphylococcal* endocarditis of the aortic valve was made and antibiotic therapy was instituted. A ruptured aortic valve cusp ne cessitated urgent replacement of the valve with a Starr Edwards prosthesis It was strongly sus pected that he continued the intravenous use of narcotics while in the hospital He was dis charged in Jan 1972 On April 15 1972 he re turned with fever chills and night sweats and admitted to continued heroin abuse He had loud systolic murmurs over his entire precordium splenomegaly, splinter hemorrhages and gross hematuria Blood cultures were positive for *P aeruginosa* and therapy was begun with gen tamicin and carbenicillin Eventually colis timethate was added, but he continued to be feb rile with positive blood cultures. He had an inter mittent diastolic murmur that changed with respiration and bounding jugular venous pulses and it was uncertain whether his endocarditis in volved the tricuspid valve the aortic prosthesis, or both Cardiac catheterization with cinean giography was performed, and revealed no dys function of the tricuspid valve Quantitative blood cultures obtained from both the right and left side of the heart at the time of catheteriza tion suggested that the prosthetic valve was the focus of infection There were 35 colony forming units per milliliter of blood in the ascending aor ta but only 6 per milliliter in right ventricular blood The organism isolated during this pro cedure was found later not to be the original *P aeruginosa*, and was identified by the CDC as *F meningisepticum*, resistant to all antibiotics but clindamycin rifampicin and vancomycin He refused surgical replacement of his prosthetic valve and therapy with these three antibiotics was begun After three months of treatment his

Table III Antibiotic therapy and outcome in six patients with *Pseudomonas* endocarditis

Patient	Age	Sex	Valve involved	Antibiotic therapy: Drugs	Antibiotic therapy: Total duration (days)	Outcome
1	29	M	Prosthetic Aortic	G Carb Colist	21	Survived *Pseudomonas* and *Flavobacterium* infections Returned one month after discharge and died of *S fecalis* endocarditis on prosthetic valve
2	39	M	Tricuspid	G Carb	39	Survived Left hospital clinically well Never kept clinic appointment
3	23	M	Tricuspid	G Carb PB	158	Survived. Valve removed and no prosthesis inserted. Died of unrelated causes one year after treatment
4	39	M	Tricuspid	G Carb Colist	178	Died. Underwent surgery for ablation of tricuspid valve Never became conscious post op Blood cultures remained positive until death.
5	33	F	Prosthetic tricuspid	G Carb	94	Survived. Prosthetic valve removed and not replaced. Doing well with negative blood cultures 3 months postoperatively
6	45	M	Tricuspid	Ceph	6	Died on fifth hospital day Blood culture negative for *Staphylococcus* but continued positive for *Pseudomonas*

G = gentamicin Carb = carbenicillin Colist = colistimethate PB = polymixin B Ceph = cephalothin

colistimethate, 300 mg per day and one received polymixin B, 120 mg per day, in combination with gentamicin and carbenicillin The sixth patient was treated with cephalothin, 8 Gm per day for *S aureus* septicemia and died before appropriate therapy for *Pseudomonas* could be instituted (Table III)

The combination of carbenicillin and gentamicin was continued postoperatively in the three patients who went to surgery The duration of postoperative antibiotic therapy was 20 days in the patient who died of continued septicemia and 28 days in each of the two patients who recovered and were cured of their infections

The organisms isolated from the five patients who received gentamicin were sensitive to this drug by Kirby Bauer disc sensitivity testing, and in two instances by serial dilution susceptibility studies Susceptibility of the organisms was also demonstrated to both polymixin B and colistimethate in the instances where these drugs were used However, in all five cases where carbenicillin was used disc sensitivity testing showed variable susceptibility of isolates from individual patients at some time during therapy

Results of therapy Even though five patients were treated with appropriate antibiotics in adequate dosages for prolonged periods, only two patients can be regarded as medical cures (Table III) One patient left the hospital apparently cured and another was cured of *Pseudomonas* infection, but blood cultures became positive for a different gram negative rod, subsequently identified by the CDC as *Flavobacterium meningisepticum*. This organism was resistant to gentamicin, colistimethate and polymixin B, antibiotics to which the *Pseudomonas* had been sensitive The other three patients did not respond to extended courses of antibiotic therapy Two of these three were eventually cured following surgical excision of the infected tricuspid valve

Three of the six patients died One of these was cured of *Pseudomonas* infection of his prosthetic valve but was later infected with *Streptococcus fecalis* and died of this infection Another died without appropriate antibiotic therapy five days after admission and gram negative rods were seen in the valve at autopsy The third patient died after surgical removal of the valve with continued positive blood cultures for *Pseudomonas* postoperatively Infection of the valve as well as a myocardial abscess were found at surgery Thus of the three patients who survived one was cured with medical therapy alone, while the other two required surgical removal of infected tricuspid valves because of refractory infection All blood

bounding and splenomegaly was present but there were no splinters or petechiae Chest x ray revealed patchy bilateral infiltrates and a cavity in the right midlung field. All eight blood cultures from admission grew *P aeruginosa*, and therapy was begun with intravenous cephalothin and intramuscular gentamicin He continued to be febrile blood cultures remained positive and pleuritic chest pain became more severe Carbenicillin was substituted for cephalothin when the nature of the organism was known but carbenicillin and gentamicin carbenicillin alone and carbenicillin with gentamicin and polymixin B failed to decrease symptoms or sterilize the blood. After four months of failure of intensive medical therapy he was taken to the operating room on June 23 1971 A very friable and thickened tricuspid valve was removed and no prosthesis was inserted. Culture of the left atrial blood at surgery yielded *P aeruginosa*, but the portion of valve cultured was sterile He did well postoperatively with no recurrence of chest pain and with increased appetite weight gain and negative blood cultures. He was discharged and was doing well one month later when he returned for his first follow up visit He was lost to follow up for nine months and died on July 22 1972 of a gunshot wound to the abdomen

Comment One possible explanation for failure of therapy in this man was late treatment because of the failure to diagnose endocarditis when it first presented. The bacteremia was not felt to originate from the heart in spite of lack of good evidence to support other sites and he was treated with only a short course of carbenicillin By the time definitive therapy was instituted, endocarditis was well established Since four months of bactericidal antibiotic therapy did not cure the infection surgery was required and appeared curative

Discussion

Bacterial endocarditis caused by *P aeruginosa* was an extremely rare disease prior to 1960 with only 32 reported cases [4,5] These consisted of nine patients who had infection of presumably normal valves eleven patients with previous valve damage secondary to rheumatic heart disease and seven patients with infection of an intracardiac foreign body following cardiac surgery Since 1960 wht spectrum of disease has changed so that virtually all of the cases have been seen either following cardiac surgery[6-9] or in drug addicts The organism is now recognized as a common contaminant of hospital equipment and a potential source of infection of intracardiac foreign bodies [10] However only recently has *Pseudomonas* endocarditis in the narcotic user reached serious proportions Reyes and co workers[11] recently reported 21 cases of *Pseudomonas* endocarditis in heroin addicts seen at the Detroit General Hospital Our findings confirm theirs and support their conclusions Their cases together with our six patients are in contrast to only 13 cases of *Pseudomonas* endocarditis out of a total of 273 cases of endocarditis in drug users gleaned from the literature [4,12-18] All of our patients and those patients reported by Reyes have been seen since 1969 and are drawn from the same geographic area

Several features in our patients are similar to those reported by Reyes The tricuspid valve was involved in five of six (83 per cent) of our patients and in 16 of 21 (76 per cent) of Reyes patients The increased frequency of tricuspid endocarditis among addicts as compared to specifically matched controls among the nonaddict endocarditis population has been noted by Cherubin and co workers [16] However they found no organism predilection for a particular valve in addicts as compared with control subjects

Two (33 per cent) of our patients were cured by medical therapy alone which is similar to Reyes experience (24 per cent) All of the patients in our series (one) and five out of six patients in Reyes series with infection of the left side of the heart died. Seven out of 21 (33 per cent) of the combined series of tricuspid valve infections responded to intensive antibiotic treatment Thus although infection of the tricuspid valve seemed to offer a better prognosis than left sided endocarditis two thirds of the patients with tricuspid endocarditis did not respond to antibiotic therapy alone

Surgery was eventually required for removal of the infected focus in three of our six patients (50 per cent) and in 12 out of 21 of Reyes patients (57 per cent) All had failed to respond to prolonged courses of antibiotics Three of Reyes patients underwent surgery with insertion of a prosthesis and another had an attempted excision of a left atrial focus of infection These four patients died of continued infection All three of our surgical patients and the remaining eight of

blood cultures became negative and he was discharged clinically well on Sept 9, 1972 He returned on Oct 21, 1972 with blood cultures positive for *S fecalis* and died soon thereafter of cerebral emboli Cultures of posthetic valve vegetations at autopsy were positive only for *S fecalis* The tricuspid valve appeared normal

Comment This remarkable patient had endocarditis with four different pathogens in ten months He survived the first three and died of the fourth caused by *S fecalis*. The last three infections were all on his prosthetic valve This illustrates the futility of inserting prosthetic valves into drug addicts who are continuing to use intravenous narcotics and also suggests the usefulness of quantitative blood cultures in conjunction with cardiac catheterization as a means of localizing the infected valve This is of particular importance with *Pseudomonas* endocarditis because the infection is often refractory to antibiotic therapy and surgical removal of the valve may be the only means of eradicating the site of infection Since addicts can infect one or several valves not known to have been previously deformed, clinical localization prior to surgery is often difficult

Patient No 2 a 38 year old male was a chronic narcotics abuser, including intravenous injection of heroin paregoric and cocaine Two months prior to admission he noted the onset of fever, night sweats bilateral pleuritic chest pain, anorexia, fatigue and dyspnea He presented on April 19 1972 with a temperature of 103° F, tachypnea, disabling chest pain and a 20 pound weight loss Physical examination revealed a characteristic murmur of tricuspid insufficiency splenomegaly, and scars of intravenous drug administration on his forearms Blood gases revealed severe hypoxemia and a chest x ray showed multiple scattered infiltrates Multiple blood cultures grew *P aeruginosa* and therapy was begun with intravenous carbenicillin and gentamicin The presumptive diagnosis was tricuspid valvulitis and septic pulmonary embolization Five days after therapy was begun he had sudden severe chest pain dyspnea and a pleural rub He gradually improved and became afebrile on May 3, 1972 Blood cultures on four occasions during therapy were negative Infiltrates on the chest x ray cavitated and slowly resolved Antibiotics were discontinued on May 30, 1972 after six weeks of treatment, and the patient was clinically well Two of six blood cultures taken when antibiotics were discontinued were positive for *Pseudomonas*, but seven subsequent blood cultures obtained over the next week were negative He was discharged on June 13, 1972 He was not suspected of using narcotics while in the hospital He never kept follow up appointments One of his friends reported to us that he was alive in early 1973, but his medical status is otherwise unknown

Comment This patient probably represents a cure with antibiotics alone It is possible that his two positive blood cultures after treatment were the result of surreptitious intravenous drug use

Patient No 3, a 23 year old man was an addict who admitted to almost daily intravenous injections He presented on Nov 17, 1970, with a one week history of hemoptysis malaise fever chills anorexia, and left sided pleuritic chest pain There were râles decreased breath sounds, and a friction rub at the left base Thrombophlebitis and cellulitis of the right arm and obvious needle marks were present Splenomegaly, splinter hemorrhages petechiae hematuria, and cardiac murmurs were not found Sputum culture grew *Diplococcus pneumoniae* and chest x ray showed a left lower lobe infiltrate with effusion Cultures from the right arm and blood grew Group A beta hemolytic *Streptococci*. Therapy was begun with intravenous penicillin, four million units per day Blood cultures repeated on Nov 22 were reported on Nov 24 as growing *P aeruginosa* in all four bottles and intravenous carbenicillin was added to penicillin He became afebrile and he felt well On Dec 5 after eleven days of carbenicillin and eighteen days of intravenous penicillin all antibiotics were discontinued A cardiac focus of *Pseudomonas* septicemia was not suspected Additional blood cultures were obtained on Dec 8, but he was discharged, receiving oral phenoxymethylpenicillin On Dec 16 one of two blood cultures was growing *P aeruginosa* but attempts to recall him for further treatment were unsuccessful

On Feb 24 1971, he presented to the hospital with several weeks of weakness shortness of breath, chills, fever pleuritic chest pain and hemoptysis On physical examination he was febrile and tachypneic with râles and a pleural rub at the right base A loud murmur characteristic of tricuspid insufficiency was heard at the lower sternal border Jugular veins were distended and

when the left side of the heart alone was involved. There was usually no radiologic evidence of cardiomegaly or congestive heart failure If the patient had received no prior antibiotic therapy all blood cultures usually grew the organism Cultures could remain positive for prolonged periods during treatment before eventual bacteriologic conversion It was remarkable how well the patient felt while continuously bacteremic Variations in the typical presentation of *Pseudomonas* endocarditis occurred where there was a mixed infection with *S aureus* In such cases the patient often presented with fulminant acute bacterial endocarditis There was nothing about the clinical presentation of *Pseudomonas* endocarditis that distinguished it from endocarditis due to other pathogens of intermediate virulence However it is important to recognize that the recovery of *P aeruginosa* from blood cultures in a drug user who does not appear very ill might represent endocarditis

Two of our patients had infection of prosthetic valves These valves had been inserted because of valve destruction secondary to bacterial endocarditis Presumably the organisms were originally introduced with intravenous narcotic injection The subsequent infection of the prosthesis was felt likely to be due to organisms injected during intravenous drug use and not to contamination at the time of surgery because blood cultures became positive four and six months after surgery and both patients admitted heavy use of drugs in the interim

The pathogenesis of *Pseudomonas* endocarditis remains obscure Infection of heart valves with gram negative organisms is unusual and infection of undamaged valves by them is exceedingly rare The organisms are undoubtedly injected intravenously as contaminants of the narcotic preparation syringe or diluent, although attempts to recover the organism from these sources have not been very rewarding [11] *P aeruginosa* is a hardy organism surviving in such common moist locations as sinks drains taps and soaps [10] This is particularly true in hospitals where the incidence of nosocomial infections with this organism is high The increasing incidence of endocarditis with this organism suggests that medical facilities may be a source of the implicated syringes fillers or diluents However frequent or continuous bacteremia with *Pseudomonas* in severely burned patients is common but rarely results in endocarditis [20,21] Thus there seems to be some predisposing factor in narcotic addicts which makes them more susceptible to endocarditis with this organism Such things as changes in hemodynamics in the right side of the heart resulting in turbulent flow or the quantity and frequency of injection of the bacteria are possible contributory factors

Both Angrist and Oka[24] and Durack and Beeson[25] have proposed that infection of heart valves with organisms of low virulence is dependent on previous disruption of the endothelial surface of the valve A sterile vegetation or roughened valve surface is produced and is then colonized by bacteria at the time of bacteremia In the narcotic addict there are several possible mechanisms of such valve damage Some materials used to cut the narcotic such as talc or starch are particulate and could cause damage to the surface of the tricuspid valve Another possibility is that bacteremia with more virulent organisms could damage the valve Such organisms may co exist with *Pseudomonas* in a polymicrobial infection If a virulent organism such as *S aureus*, is not present in large numbers it may be supplanted on the valve surface by *Pseudomonas*. This is particularly true if antibiotics are administered by the patient or a local physician suppressing the original pathogen and allowing *Pseudomonas* to flourish Rabin and coworkers[23] reported three cases of *Pseudomonas* endocarditis in burned patients following *Pseudomonas* septicemia In all three cases the *Pseudomonas* septicemia had followed prolonged *Staphylococcal* septicemia or was coincident with it In one case both *P aeruginosa* and *S aureus* were recovered from an aortic vegetation at postmortem examination In four of the 21 narcotics users in Reyes series both *P aeruginosa* and *S aureus* were recovered from the blood at some time during hospitalization In three of our patients organisms known to cause damage to normal heart valves were isolated from the blood on admission to the hospital Group A beta hemolytic *Streptococcus* *S fecalis* and *S aureus* were grown from the blood one to thirteen days before the first culture became positive for *Pseudomonas* Since two other patients in our series had their infection on prosthetic valves there remains only one patient with normal valves who had *Pseudomonas* as the sole organism isolated from blood cultures

Reyes' patients had removal of the tricuspid valve without insertion of a prosthesis Eight (73 per cent) of these patients survived and were free of infection when last seen We treated our patients for one month with appropriate antibiotics postoperatively

There is little to offer the addict with left sided *Pseudomonas* endocarditis who does not respond to medical therapy Reinfection of inserted prostheses has been very frequent among drug users as observed in Reyes' patients and in ours However total ablation of the tricuspid valve is well tolerated and offers an excellent opportunity for salvaging the patient with an infected tricuspid valve who has not responded to conventional therapy [17]

Antibiotic therapy with a combination of gentamicin and carbenicillin was used in five out of six (83 per cent) of our patients and in 17 out of 21 (81 per cent) of Reyes patients In neither series could the success of medical therapy alone be predicted on the basis of drug dosage duration of therapy or in vitro antibiotic susceptibility In our study, variable resistance and sensitivity of the same organism to carbenicillin, as tested by the disc sensitivity method was noted in all patients There is evidence that some organisms found resistant by use of the standard 50 microgram carbenicillin disc currently recommended by the Food and Drug Administration (FDA) may be found to be susceptible by the serial broth dilution method (susceptibility defined as a minimal inhibitory concentration of equal to or less than 100 micrograms per milliliter) The use of a 100 microgram disc is reported to markedly reduce the discrepancies between the two susceptibility testing methods [18] In Reyes' series organisms from five out of six patients who responded to medical therapy alone had a minimal inhibitory concentration of 100 micrograms per milliliter or greater as determined by the serial broth dilution method These organisms would have been determined resistant by the disc diffusion method, using even the 100 microgram disc Thus the correlation between in vitro testing and in the vivo efficacy of carbenicillin in treating *Pseudomonas* endocarditis is unclear There may be in vivo synergism between carbenicillin and gentamicin to explain the apparent efficacy of this combination in treating some of the patients [19]

The clinical presentation, physical findings and course of the illnesses were similar in the majority of the cases in both series The typical patient was a black male heroin addict under forty years of age who presented with a history of several weeks or months of malaise, anorexia, and weight loss The symptoms were more suggestive of subacute than acute bacterial endocarditis Chest pain or chills were usually responsible for the patient seeking medical help On physical examination, fever was invariably present but vital signs were otherwise normal A murmur of tricuspid insufficiency was usually present, but meticulous auscultation was required because these murmurs were soft and changeable Banks, Fletcher and Nayab[14] have recently reported on 50 patients with heroin associated endocarditis, 42 of whom had tricuspid involvement. In 16 of these 42 patients with tricuspid regurgitation, the tricuspid murmur was not present or not recognized at the time of admission In two patients an atrial diastolic gallop, a ventricular diastolic gallop or a systolic click, heard over the left lower sternal border and external jugular vein preceded the late appearance of typical murmurs of tricuspid insufficiency

Cardiac catheterization may be necessary to delineate valvular dysfunction in some patients with minimal auscultatory signs, particularly if cardiac surgery is contemplated If catheterization is performed, quantitative blood cultures from both the right and left sides of the heart may be an additional method of localizing the site of infection to a particular valve This is exemplified by one of our patients (Patient No 1) in whom quantitative blood cultures suggested that the prosthetic aortic valve and not the tricuspid valve was infected This was confirmed at autopsy

Splenomegaly was common in our series (Table I) but uncommon in Reyes series Peripheral manifestations of endocarditis such as petechiae, Roth s spots and hematuria were rarely seen Scars produced by multiple intravenous infections were usually found when diligently sought The white blood cell count was not often helpful Although it was often above 10,000 per cubic millimeter there was frequently no increase in the percentage of neutrophils or band forms Chest x rays showed multiple infiltrates, frequently but not always cavitary which represented septic emboli These were not present

Evaluation of mitral regurgitation in endocardial cushion defect by selective left ventriculography with reference to surgical intervention on mitral valvular cleft

Kenji Okamura M D
Tatsuhiko Kudo M D
Hitoshi Kovanagi M D
Yasuharu Imai M D
Souji Konno M D
Tokyo Japan

Selective left ventriculography is of value in evaluating the extent of mitral insufficiency As the contrast medium injected into the left ventri cle opacifies the left atrium in accordance with the severity of the mitral insufficiency the ex tent of the mitral regurgitation has been evalu ated through comparison with degrees of opacifi cation of the left ventricle the ascending aorta and the left atrium in cases without interatrial communication [1 4] In cases with endocardial cushion defect however as the contrast medium regurgitated into the left atrium also opacifies the right heart by interatrial communication the conventional criteria used for cases without interatrial shunt is inapplicable

The purpose of this report is (1) to present a method for evaluating the degree of mitral in sufficiency using selective left ventriculography in cases with an incomplete form of endocardial cushion defect and (2) to consider appropriate operative methods for mitral cleft with different degrees of severity of mitral regurgitation

Materials and methods

Forty patients with an incomplete type of en docardial cushion defect associated with mitral insufficiency underwent corrective surgery with the aid of cardiopulmonary bypass during the period Aug 1 1966 to Dec 15 1973 The patients consisted of 15 males and 25 females ranging in age from 1½ to 42 years

Selective left ventriculography was performed preoperatively and the anatomic diagnosis of an incomplete form was ascertained during the in tracardiac procedure in each case The incom plete form is defined as having a cleft mitral valve varying degrees of hypoplasia or tricuspid valve cleft without ventricular septal defect and continuity of valvular tissue above the ventricu lar septum between the anterior and posterior halves of the atrioventricular valve

The angiocardiographic features in all cases were studied for the purpose of evaluating the ex tent of mitral regurgitation concerning the following points (1) presence or absence of the regurgitant jet (2) the degree of opacification of both atria and the pulmonary arterial trunk and (3) comparison of the degree of opacification of both atria and the pulmonary arterial trunk with that of the ascending aorta Comparison of the degree of opacification of these portions was made at the time when the descending aorta was visualized down to the diaphragmatic level for the sake of standardization because the density of contrast media was generally most adequate for comparison just before the abdominal aorta was opacified Also we used the angiocar diographic anteroposterior projection films for

F om the D p rtm nt f Surg ry The He rt Institute of Jap n Tokyo Womens M d l C ll ge T kyo Jap n

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The financial drain on society that the addict represents is exemplified by our patients The stubborn and refractory illness leading to pro longed hospitalization in five of the six patients produced an average hospital bill of $31,000 with a range of $7,000 to $42 000

Summary

Six intravenous heroin users with *P endocar ditis* were seen between 1970 and 1972 Five out of six (83 per cent) had tricuspid valvulitis Fever and a significant murmur were found in all cases, a subacute presentation and splenomegaly were found in 83 per cent, and chest pain with cavitat ing infiltrates on x ray was observed in 67 per cent Three patients died of infection Three pa tients survived, one was cured with medical therapy alone, and two required surgical removal of the infected valve as well The success of surgi cal ablation of the tricuspid valve in these pa tients is encouraging particularly in view of their poor response before surgery to combina tions of antibiotics with proved in vitro efficacy Prior bacteremia with more virulent organisms may be important in the pathogenesis of en docarditis with *Pseudomonas*

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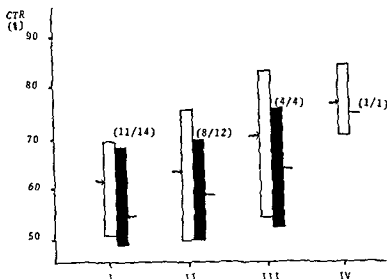


Fig 3 Pre and postoperative CTR distribution in each degree of regurgitation CTR cardiothoracic ratio ( ) number of patients with decreased CTR out of cases alive postoperatively Arrows stand for the mean CTR in each regurgitation. □ preoperative CTR distribution ■ postoperative CTR distribution.

tricular septa in all cases are situated in almost parallel to the frontal plane at an angle of about 10 degrees and 83 per cent of the atrial septa are aligned in almost the same direction toward the frontal plane Thus in cases with endocardial cushion defect as both the atria are overlapped in anteroposterior projection in the majority of cases we can evaluate the degree of opacification of overlapped atria in this projection

The severity of mitral insufficiency is graded as follows Grade I regurgitant jet into the left or right atrium is shown without opacification of the pulmonary arterial trunk Grade II both atria are outlined almost completely with faint opacification of the pulmonary arterial trunk Grade III both atria and the pulmonary arterial trunk are densely opacified but yet thinner than the dye density in the ascending aorta Grade IV both atria and the pulmonary arterial trunk are opacified as intensely as the ascending aorta (Fig 2)

In order to prove their validity our criteria are compared with the following clinical findings (1) auscultatory findings of mitral regurgitant murmur (2) cardiothoracic ratio (3) the extent of left atrial enlargement judged by the prominence of the left atrial appendage on the left heart border in anteroposterior projection and the deviation of the barium filled esophagus in right anterior oblique projection and (4) catheterization data especially left atrial pressure right ventricular pressure or left to right shunt ratio

Table I Number of patients and mortality rate for each degree of regurgitation

Grade of regurgitation	*No. of patients*	*No of deaths*	*Mortality rate (%)*	
IV	2	1	50	44
III	7	3	43	
II	15	3	20	16
I	16	2	12	

Results

Forty patients were classified as follows (Table I) Grade IV 2 cases Grade III 7 cases Grade II 15 cases and Grade I 16 cases. On auscultation in those with Grade III or Grade IV regurgitation a Grade 3/6 to 4/6 systolic regurgitant murmur is heard at the apex whereas in patients with Grade II or Grade I regurgitation the intensity of the murmur varies from Grade 2/6 to 3/6 in the majority of cases Mid diastolic murmur along the lower sternal border or at the apex and the splitting of the pulmonary second sound are general findings regardless of the severity of regurgitation The cardiothoracic ratio has a

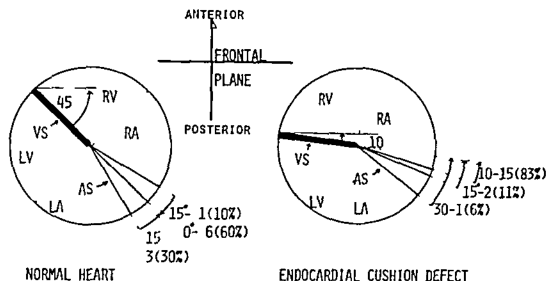


Fig 1 Schematic presentation of the positional relationship of the atrial and ventricular septa with the frontal body plane comparing the 10 normal hearts with 18 cases of endocardial cushion defect from the autopsy findings Abbreviations: VS ventricular septum AS atrial septum RV right ventricle LV left ventricle LA left atrium and RA right atrium

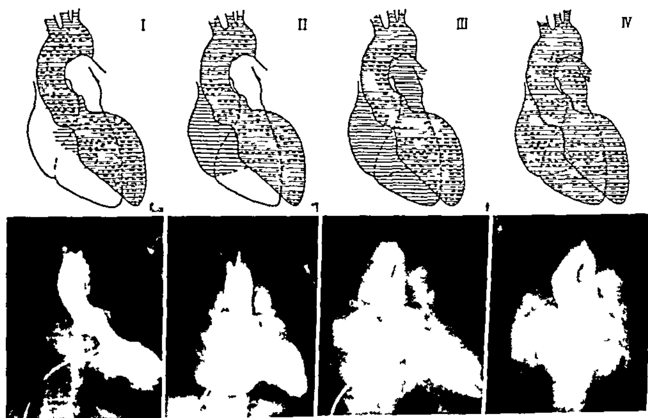


Fig 2 Schematic and angiocardiographic features of representative cases in each degree of mitral regurgitation For details of classification see text

these comparative studies for the following reasons From the studies of 18 autopsied cases with endocardial cushion defect and 10 autopsied normal hearts at our institute the mutual interrelationships of the atrial and ventricular septa were depicted as their angles to the frontal body plane (Fig 1) The ventricular septa in all normal hearts are placed obliquely extending from right posterior to left anterior direction at an angle of 45 degrees to the frontal body plane Sixty per cent of the atrial septa are located in such a manner and 30 per cent of them are deviated posteriorly by an angle of 15 degrees while in the cases with endocardial cushion defect the ven

Table II Postoperative course of the patients repaired with various operative methods

Operative methods		Grade of regurgitation	No of patients	CTR decreased in	LAE	Hospital deaths
1	Cleft left unsutured	I	10	7	1	1
		II	7	3	1	3
		III	1	0	0	1
		IV	0			
2	A few stitches applied at the base	I	6	4	0	1
		II	6	4	1	0
		III	4	4	1	0
		IV	1	0	0	1
3	Complete closure	I	0			
		II	2	1	1	0
		III	0			
		IV	0			
4	Pericardial patch application	I	0			
		II	0			
		III	1	0	0	1
		IV	1	1	0	0
5	Prosthetic valve replacement	I	0			
		II	0			
		III	1	0	0	1
		IV	0			

CTR cardiothoracic ratio LAE, left atrial enlargement

As shown in Table I there were five hospital deaths (16 per cent) out of 31 cases with Grade II or Grade I regurgitation and four deaths (44 per cent) in nine cases with Grade III or Grade IV regurgitation In the patients with Grade I to Grade II regurgitation for which methods 1 or 2 were applied, there were five hospital deaths out of 29 (17 per cent) Follow up studies were made in 24 patients ranging from 2 months to 7 years after operation There was a decrease in cardiothoracic ratio in 75 per cent (18/24) Seventy one per cent of the cases (17/24) showed symptomatic improvement and greater exercise tolerance In cases with Grade III regurgitation repaired by method 2 all four cases are alive and have a decrease in cardiac size However severe hemolytic anemia indicative of persistence of significant mitral regurgitation was complicated in three out of four cases in the immediate postoperative period and lasted for about two months In the group repaired by method 3 both cases are alive but one case with Grade II regurgitation remains in a state of moderately severe heart failure due to exacerbation of mitral insufficiency after operation A chest x ray film of this case shows a markedly dilated left atrium In the group repaired with methods 4 or 5 one case of Grade IV regurgitation repaired with method 4 is alive and a decrease of cardiac size is recognized

Exacerbation of the mitral regurgitation was responsible for postoperative left atrial enlargement in five patients including one case of Grade III three cases of Grade II and one case of Grade I Two cases are repaired by method 1 two cases by method 2 and one case by method 3

Discussion

It has been considered by many authors that an angiocardiographic assessment of the degree of mitral valvular incompetence in endocardial cushion defect is difficult since the contrast media are not confined within the left atrium in contrast with mitral valvular incompetence with an intact atrial septum Although its assessment is possible to some extent by other information obtained from the electrocardiogram cardiothoracic ratio left atrial enlargement on chest roentgenogram auscultatory findings and intracardiac finger palpation prior to the institution of cardiopulmonary bypass [9 13] the more reliable quantitative method for mitral regurgitation is necessary since the degree of mitral incompetence determines the prognosis

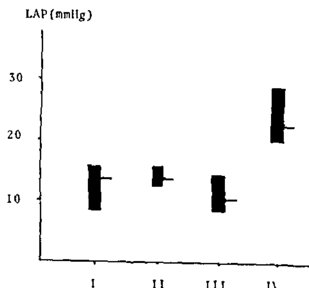


Fig 4 Left atrial pressure distribution in each degree of regurgitation LAP maximum pressure of left atrial V wave Arrows stand for mean LAP

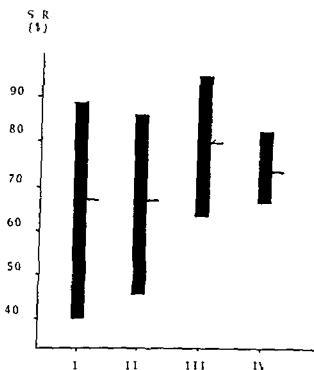


Fig 5 Shunt ratio distribution in each degree of regurgitation SR left to right shunt ratio Arrows stand for mean SR in each regurgitation

good correlation with this angiocardiographic classification of mitral regurgitation as shown in Fig 3 Those patients with Grade IV regurgitation have increases in amplitude of the left atrial V wave while in patients with less than Grade III regurgitation no definite relationship is found between the degree of regurgitation and left atrial pressure (Fig 4) Those with more than Grade III regurgitation show left atrial enlargement in the majority of cases Amounts of left to



Fig 6 Angiocardiogram in a case of complete form as viewed in the lateral projection The regurgitant jet through interventricular communication is visualized with opacification of the right ventricular outflow tract and pulmonary arterial trunk in an early phase The film is taken two seconds after injection of the contrast medium

right shunt or right ventricular pressures have no correlation with the severity of mitral insufficiency (Fig 5)

This angiocardiographic classification of mitral regurgitation correlates well with the clinical severity of the patients condition in almost all cases in each degree, with a few exceptions

Postoperative follow up results Our policy of surgical intervention on the mitral valvular cleft in endocardial cushion defect includes (1) simple closure of the primary defect without direct intervention on the valve (2) a few interrupted stitches applied near the base of the cleft (3) complete closure of the cleft to the free margin of the leaflet (4) pericardial patch application to close the gap and (5) prosthetic valve replacement (Table II)

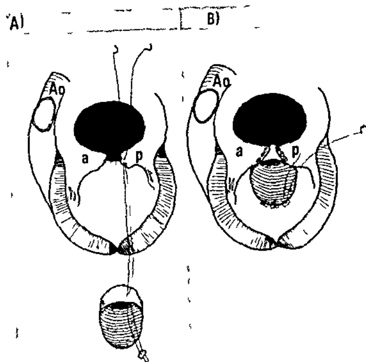


Fig 8 Illustration of a new operative method for a defective mitral valve using a monocusp heterograft aortic valve The monocusp heterograft is sutured on the inner surface of the Dacron graft and trimmed in a tear drop ped shape as shown in the figures The length of the graft beneath the heterograft is about 1 0 to 1 5 cm This length permits enough clearance from the conduction pathway in suturing its lower margin to the septal surface of the left ventricle (Fig 5 *B*) The cleft is repaired by placing a monocusp heterograft valve underneath the mitral valve with its convex surface toward the left atrium Abbreviations Ao ascending aorta a anterior com mon leaflet and p posterior common leaflet

contrast medium (Fig 6) yet the opacification of those portions through mitral regurgitation is delayed by ½ to 1½ seconds as shown in Fig 7 *A* and *B*

Thus the diagnosis of the complete form can be made by recognition of regurgitant contrast medium through ventricular septal defect which selectively opacifies the right ventricular outflow tract and pulmonary arterial trunk rather pre maturely in the early phase described above

According to many reports in the literature the anterior mitral cleft observed in patients with an endocardial cushion defect has been treated surgically in such a way with an applica tion of two or three interrupted stitches when ever it is encountered,[13 17 19] or only when it is complicated with mitral insufficiency [11,20 24] From the study of our long term follow up results of surgically treated cases with an incomplete form of endocardial cushion defect, almost all cases with a Grade I or Grade II regurgitation which were repaired with such methods as leaving a cleft unsutured or applying a few interrupted stitches near the base of the cleft have a marked clinical improvement however, these methods when applied on patients with Grade III or Grade IV regurgitation generally end in less favorable clinical results such as hemolytic anemia or con gestive heart failure with exacerbation or persis tence of mitral regurgitation Occasionally, se verity of mitral regurgitation justifies prosthetic valve replacement however in view of the fact that regurgitation in endocardial cushion defect is solely caused by valvular tissue defect or valvu lar immobility in the anterior mitral leaflet or the fact that mitral valve replacement in early childhood is not recommended in the long run more conservative yet effective measures should be investigated Therefore we are performing laboratory evaluations of a new method in which the cleft is repaired by placing a monocusp heterograft valve underneath the mitral valve with its convex surface toward the left atrium in such a way as described in Fig 8

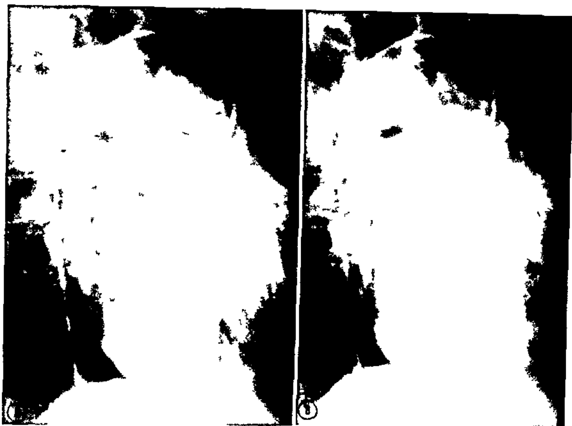


Fig 7 A and B Lateral angiocardiogram in a case of complete form with severe mitral insufficiency *A*, The right ventricular outflow tract and the pulmonary arterial trunk are opacified through the interventricular communication (arrow) in an early phase which is two seconds after the injection *B* Opacification of the right ventricle and pulmonary arterial trunk through mitral regurgitation is delayed by ¾ second compared with opacification through interventricular communication

and also determines the surgical approach and outcome

In our presented method, differentiation between the incomplete and complete form is mandatory because the pulmonary arterial trunk is opacified by the contrast media through both atrial and ventricular left to right shunt in the presence of the ventricular septal defect The complete form is confirmed only when the contrast medium in the lateral plane passing directly from the left ventricle to the right ventricle through a ventricular septal defect is seen, because the left ventricular angiocardiographic appearance is considered to be basically the same in all varieties of endocardial cushion defect, except the cases with a free floating anterior common leaflet (Rastelli s Type [14]C or Tenckhoff's Type [15]I) which demonstrates a peculiar right angled appearance of the left ventricular outflow tract in diastole yet the absence of a typical serrated appearance and the deep indentation in systole [16] On interpretation of the angiocardiographic films from the viewpoint of the differential diagnosis between the two types, it is necessary to consider that a false positive angiocardiographic diagnosis of interventricular communication may be made because the jet of mitral regurgitation is commonly directed anteriorly and laterally toward the right atrium giving a spurious appearance to the ventricular septal defect on lateral angiocardiography Rastelli Kirklin and Kinkaid[16] reported that a false positive angiocardiographic diagnosis was made in five out of 18 cases of the partial form (28 per cent) Also a false negative diagnosis of the absence of interventricular communication may be made because interventricular communication may be obscured by the associated mitral regurgitation directed into the right atrium However, in an analysis of angiocardiographic features in 13 cases with the complete form it is demonstrated that the regurgitant jet of interventricular communication selectively opacifies the right ventricular outflow tract and the pulmonary arterial trunk in an early phase between 1¾ and 2½ seconds after injection of the

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Summary

New criteria for the evaluation of mitral regurgitation associated with endocardial cushion defect using selective left ventriculography are presented The severity of the regurgitation is classified into four groups namely Grades I to IV by comparing degrees of opacification of both atria and the pulmonary arterial trunk with that of the ascending aorta Validity of this criteria is substantiated with clinical findings and operative methods for the mitral cleft are discussed from the viewpoints of the degree of regurgitation and the postoperative follow up results

Those with more than a Grade III regurgitation show left atrial enlargement in the majority of cases Those with Grade IV regurgitation have increases in the amplitude of left atrial V wave while in patients with less than Grade III regurgitation no definite relationship is found between the degree of regurgitation and left atrial pressure The cardiothoracic ratio has a good correlation with an angiocardiographic classification of mitral regurgitation On auscultation of those cases with Grade III or Grade IV regurgitation a Grade 3/6 to 4/6 systolic regurgitant murmur is heard at the apex whereas in patients with a Grade II or Grade I regurgitation intensity of the murmur varies from Grade 2/6 to 3/6

This angiocardiographic classification of mitral regurgitation correlates well with the clinical severity of the patients condition

Our policy of surgical intervention on the mitral cleft in endocardial cushion defect includes (1) simple closure of the primary defect without direct intervention on the valve (2) a few interrupted stitches applied near the base of the cleft (3) complete closure of the left cleft to the free margin of the leaflet (4) pericardial patch application to close the gap and (5) prosthetic valve replacement Although marked clinical improvement is seen in patients with Grade I or Grade II regurgitation repaired with methods 1 2 or 3 these methods when applied in patients with Grade III or Grade IV regurgitation generally end in less favorable clinical results such as hemolytic anemia or congestive heart failure with persistence of the regurgitation One case of Grade IV regurgitation repaired with method 4 has a good clinical result

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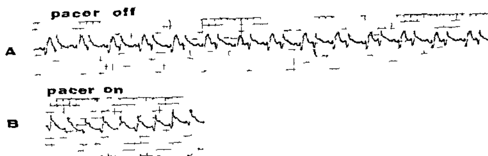


Fig 1 *Case 1* Pacing catheter—induced bigeminy in a 43 year-old man suffering from an acute myocardial infarction. *A* when the pacer is off every conducted beat is followed by an ectopic beat The coupling interval varies continuously between 0 30 and 0 42 sec The atrial rate is 120 *B* now the pacer is turned on at a rate of 111 The paced beats have a configuration very similar to the ectopic beats of strip A Note the retrograde P wave immediately after the peak of R

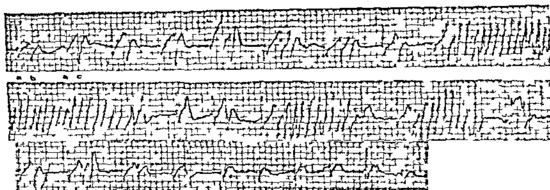


Fig 2. *Case 3* Continuous strip monitor lead Catheter induced ectopic activity and ventricular flutter fibrillation. There are three types of beats Beats *a* are probably of nodal origin Beats *b* and *c* are interpolated bifocal ventricular ectopic beats The ectopic activity *degenerates into* short runs of ventricular flutter fibrillation three times. The electrode was removed from the ventricle while the bottom line of the strip was being taken Note the atrial ectopic beat following the first nodal beat after the last ventricular ectopic beat

despite adequate treatment with lidocaine A chest x ray revealed that the intracardiac catheters had maintained their initial positions Intravenous procainamide was then administered. The patient received 1 Gm of the drug during a two hour period with no significant improvement The pacemaker was then activated and a rhythm strip revealed that the paced beats had a configuration very similar to the ventricular ectopic beats (Fig 1 *B*) The threshold for stimulation had increased from 0 3 ma to 0 5 ma The diagnosis of catheter induced arrhythmia was confirmed with cessation of ectopic activity when the electrode was withdrawn

Case 2 A 68 year old retired physician was admitted for syncope Physical examination revealed mild pulmonary edema The ECG showed complete heart block with a nodal rhythm rate 54 and signs of an acute inferior myocardial infarction A flow directed catheter was placed in the pulmonary artery and an electrode was placed in the right ventricle and connected to a demand pacemaker Several hours later ventricular ectopic activity appeared at a frequency of 10 to 15 beats per minute which had a varying coupling interval and remained unresponsive to treatment The pacemaker was then activated and the ventricles were continuously stimulated The paced beats had the same configuration as the spontaneous ectopic beats The diagnosis of catheter induced arrhythmia was made The electrode was repositioned with cessation of the ventricular ectopic activity

Case 3 A 73 year old woman was admitted following a syncope spell Her ECG revealed an idioventricular rhythm at a rate of 35 A ventricular electrode was inserted and connected to a demand pacemaker set to be inhibited by a rate above 50 per minute On the third hospital

Catheter-induced arrhythmias

Panos C Voukydis M D , Ph D
Stafford I Cohen, M D
Boston, Mass

It is frequently stated that intracardiac foreign bodies such as an electrode catheter, a central venous line, or a pulmonary artery catheter that migrates to the ventricle may give genesis to arrhythmias[1,2] Such arrhythmias are difficult to treat if their origin is not promptly recognized. The present report describes six cases of catheter induced arrhythmias that occurred in the Medical Intensive Care Unit of the Beth Israel Hospital during a period of eight months

Materials techniques and clinical observations

During eight consecutive months 72 flow directed pulmonary artery catheters and 80 temporary transvenous ventricular pacemakers were introduced in 106 patients admitted to the Medical Intensive Care Unit The criterion for insertion of pulmonary artery catheters was acute myocardial infarction with unstable hemodynamics including cardiogenic shock and hypotension in patients with acute or chronic respiratory problems The criteria for insertion of temporary ventricular pacemakers were as follows complete heart block, second degree A V block associated with Stokes Adams attacks new bifascicular or trifascicular block in the presence of an acute myocardial infarction ventricular ectopic activity requiring ventricular overdrive suppression, and hypotension in conjunction with a very slow supraventricular rate In addition patients undergoing intra aortic balloon counterpulsation routinely received a ventricular transvenous pacing electrode and a flow directed pulmonary artery catheter The flow directed catheters were usually inserted via a cutdown to an arm vein and they were advanced to the pulmonary artery under pressure control or under fluoroscopic control The temporary electrodes were usually inserted via the transfemoral route and were advanced to the right ventricular apex under fluoroscopic control On a few occasions an arm vein was used for insertion of the electrode Introduction of a flow directed catheter into the right ventricle was only rarely associated with ventricular ectopic activity In contrast introduction of the temporary electrode into the right ventricle was usually associated with ventricular ectopic activity in the form of ventricular ectopic beats or, rarely short runs of ventricular tachycardia In the latter event, the electrode was withdrawn to the right atrium and then repositioned The electrode placement was considered to be satisfactory when threshold for stimulation was less than 1 5 ma and there was no catheter induced ventricular ectopic activity Five patients with temporary pacemakers and one with a flow directed pulmonary artery catheter developed ventricular ectopic activity within several hours to three days following the catheter placement

Case 1 A 43 year old man was referred from another hospital for treatment of an extensive anterior myocardial infarction Upon admission he was mildly hypotensive and his electrocardiogram (ECG) showed evidence for a new right bundle branch block and left posterior hemiblock that did not exist in the tracing submitted from the referring hospital A flow directed catheter was placed in the pulmonary artery and an electrode was advanced to the apex of the right ventricle and connected to a standby pacemaker The mild hypotension was treated successfully with volume replacement Two hours later, ventricular ectopic activity appeared which, within one hour, evolved into continuous bigeminy with nonfixed coupling (Fig 1 *A*)

From the Department of Medicine Beth Israel Hospital and Harvard Medical School Boston Mass

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Reprint requests Dr P C Voukydis Beth Israel Hospital 330 Brookline Ave Boston Mass 02215

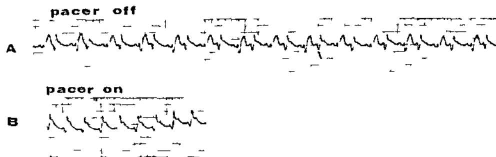


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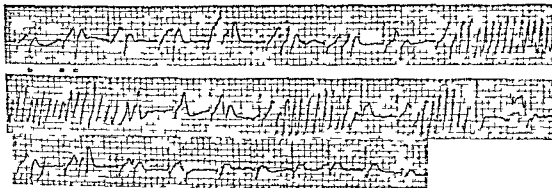


Fig 2 *Case 3* Continuous strip monitor lead Catheter induced ectopic activity and ventricular flutter fibrillation. There are three types of beats Beats *a* are probably of nodal origin Beats *b* and *c* are interpolated bifocal ventricular ectopic beats The ectopic activity degenerates into short runs of ventricular flutter fibrillation three times. The electrode was removed from the ventricle while the bottom line of the strip was being taken. Note the atrial ectopi beat following the first nodal beat after the last ventricular ectopic beat

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Fig 3 *Case 6* Continuous strip Lead V_1 Catheter induced isorhythmic dissociation in a 67 year-old man with acute myocardial infarction and papillary muscle dysfunction There are four kinds of beats Beats *a* are wide (QRS = 0 16 sec) and are always preceded by a P wave and a P R interval varying between 0 04 and 0 08 sec Beats *b* have a completely different configuration and are not preceded by P waves Beats *c* are always preceded by a P wave and a P R interval of 0 16 sec Beats *d* are similar in configuration to beats *a*, but are not preceded by P waves and appear to be interpolated between two *a* beats The *a* beats cannot be the result of a repetitively firing ventricular ectopic focus because the R R interval varies widely Fluoroscopy showed that the flow directed catheter was displaced inside the right ventricle with a large loop in the right atrium Every atrial contraction caused a forward thrust of the catheter Thus it appears that the *a* beats were catheter induced

day, the pacemaker was not sensing properly and was turned off while a repositioning of the electrode was planned in the same day A few hours later ventricular ectopic activity was noted with coupling intervals varying between 0 44 and 0 52 sec In spite of an infusion of lidocaine the ectopic activity increased There were salvos of 2 to 3 ventricular ectopic beats followed by three short runs of ventricular flutter which terminated spontaneously (Fig 2) The pacing wire was withdrawn to the right atrium and all ectopic activity ceased

Case 4 A 66 year old patient, in cardiogenic shock following an acute anterior myocardial infarction was being treated with the intra aortic balloon pump (IABP) As part of our established routine, he had placement of a flow directed pulmonary artery catheter and a transvenous ventricular electrode On the second day of counterpulsation, ventricular ectopic activity was noted at a rate of 10 to 12 ventricular ectopic beats per minute The pacing threshold was found unchanged and the paced beats, although exhibiting a left bundle branch block pattern, had a distinctly different configuration from the ectopic beats Lidocaine treatment was started and was ineffective It was then noted that the ectopic beats occurred during deep inspiration Fluoroscopy showed that the electrode formed an excessive loop inside the right ventricle during inspiration The wire was withdrawn to the right atrium and the ectopic activity ceased

Case 5 A 54 year old woman was admitted with an acute inferior myocardial infarction On the second hospital day she exhibited Mobitz Type II A V block and a temporary transvenous pacemaker was inserted and placed on standby demand mode Twelve hours later the pacemaker started sensing erratically with resulting intermittent competition between the intrinsic rhythm and the pacemaker rhythm When the pacer was turned off it was noted that there were frequent ventricular ectopic beats with the same configuration as the paced beats The diagnosis of catheter induced arrhythmia was then considered Repositioning of the pacing wire resulted in abolition of the ectopic activity and proper sensing

Case 6 A 67 year old man was admitted for treatment of an acute myocardial infarction Physical examination revealed a moderate degree of left ventricular failure and a new apical systolic murmur A flow directed catheter was placed into the pulmonary artery for monitoring of the wedge pressure On the third hospital day, marked ventricular ectopic activity was noted which at times appeared to be an accelerated idioventricular rhythm with isorhythmic dissociation (Fig 3) Therapeutic doses of lidocaine and procainamide failed to suppress the ectopic activity It was then noted that the damped pressure tracing from the flow directed catheter assumed a right ventricular pressure configuration after it was flushed Fluoroscopy showed the tip of the catheter to be in the right ventricle and a large loop in the right atrium Ev

ery atrial contraction caused a forward thrust of the catheter which presumably caused mechanical stimulation of the right ventricle Removal of the catheter resulted in cessation of the ventricular ectopic activity

Discussion

It is well established that intraventricular catheters may cause ventricular ectopic activity or even ventricular tachycardia [1,2] This is illustrated dramatically by Case 3 of the present paper (Fig 2) It is equally true that an arrhythmia may occur independent of an intracardiac foreign body Incorrect diagnosis of arrhythmia from an intraventricular catheter may lead to its unnecessary removal thereby resulting in deprivation of a potentially lifesaving measure It seems that establishing the basis for criteria that can help diagnose a catheter induced arrhythmia might be of assistance to the staff of intensive care units

Arrhythmias which are induced during catheter placement are very frequent Paulk and Hurst[4] had nine cases of ventricular fibrillation occur during pacemaker placement among 43 patients with complete heart block Rutherford McCann and O Donovan[5] noted frequent ventricular ectopic beats and two cases of ventricular tachycardia during placement of polyethylene catheters in the pulmonary artery in a series of 28 patients The use of flow directed catheters in contrast, is associated with lower incidence of ventricular ectopic activity [6] Our experience with bedside flow directed pulmonary artery catheterization is in agreement It appears however that placement of the catheter under pressure guidance alone may result in excessive loops of catheter within the right ventricle or more commonly the right atrium Our experience with placement of transvenous electrodes in the right ventricle under fluoroscopic control has indicated that uncomplicated ventricular ectopic activity can be expected during placement Fortunately the arrhythmias are only transient and we have not had to use electric shock to terminate an abnormal rhythm

The diagnosis of arrhythmias that are induced during catheter placement should be as obvious as the remedy Our present series shows that the incidence of late catheter induced arrhythmias is approximately 6 per cent It appears however that this relatively high frequency is related to temporary electrodes and pulmonary artery catheters Permanent electrodes have not been reported to cause mechanically induced ventricular ectopic activity despite the relatively high incidence of catheter dislodgement [7,11] The cases of catheter induced arrhythmias herein presented illustrate the potential complexity of these arrhythmias They also give a number of useful clues from which diagnostic principles can be constructed In all cases the arrhythmia developed following the placement of catheters a fact which should arouse the suspicion of a catheter induced arrhythmia Another clue is ineffectiveness of anti arrhythmics especially when given in high doses An additional aid to diagnosis is demonstration of displacement of the catheter from the initial position If the catheter in question is a pacing wire additional information can be obtained by noting ineffective sensing and an increase in pacing threshold Erratic sensing and an increased threshold are probably due to a displacement of the catheter It is also very useful to activate the pacemaker and compare the paced beats with the ectopic beats if they are similar the chances are that the ectopic beats are mechanically induced by the catheter Another observation of the present series is the presence of widely varying coupling intervals Cases 4 and 6 were unusual the former showing ectopic activity only during inspiration whereas the latter demonstrated a very complicated arrhythmia that could not be explained on the basis of known principles Three cases similar to our Case 6 have been presented by Massumi and Ali [12]

The principles and criteria for diagnosis of catheter induced arrhythmias can be summarized as follows (1) the arrhythmia begins after a catheter has been placed in the right ventricle The presence of dislodged catheters excessive intracardiac loops of catheters central displacement of central venous lines or intracardiac fragments of polyethylene catheters should be sought by careful inspection of a chest x ray taken after the arrhythmia has begun (2) If the catheter in question is an electrode usually there is a concomitant failure to sense properly and the threshold may increase The paced beats usually look very much like the ectopic beats (3) The ectopic beats have in general a left bundle branch block configuration If they appear in the form of bigeminy the coupling interval may vary widely (4) High doses of anti arrhythmic medications

may be ineffective (5) Occasionally, the arrhythmias are complicated and hard to explain on the basis of established principles (6) Finally, the *ultimate test for diagnosis of a catheter induced* arrhythmia is cessation of the arrhythmia following removal or repositioning of the catheters

Summary

Catheter induced arrhythmias which occurred several hours to several days following successful placement of temporary transvenous right ventricular electrodes or flow directed pulmonary artery catheters were observed in six out of 106 patients The arrhythmias took the form of ventricular bigeminy, ventricular tachycardia and in one instance isorhythmic dissociation *These arrhythmias were resistant to high* doses of antiarrhythmic medication The diagnosis can be suspected by noticing an excessive catheter loop or an altered catheter position in the chest x ray or by observing faulty sensing erratic pacing or an increased threshold for ventricular stimulation Corroborative evidence can be obtained from the electrocardiogram where the catheter induced depolarizations usually take a left bundle branch block pattern and the coupling interval of the ectopic beats *may vary widely* Some pacing catheter induced beats resemble the paced beats in configuration In other cases the rhythm cannot be explained by established principles The diagnosis of catheter induced arrhythmia is confirmed when the arrhythmia ceases following removal or repositioning of the catheter

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Continuous recording of the vectorcardiogram in acutely ill patients

Morrison Hodges M D
Toshio Akiyama, M D
Theodore L Biddle M D
W Bromley Clarke Ph D
Douglas L Roberts M D
Marvin W Kronenberg M D
Rochester N Y

Electrocardiographic monitoring of acutely ill patients has usually been accomplished with a single lead. Three or four electrodes are usually employed, and electrode placements have been suggested[1] which maximize the P and QRS complexes in the lead Single lead systems are usually adequate for rhythm analysis However such systems necessarily give information in only one electrical plane and thus information present in other electrical planes is not available Furthermore analysis of the QRS complex and ST segment with respect to axis orientation pathologic Q waves ST segment elevation etc is usually not possible in a single lead system In view of these considerations we adapted a standard vectorcardiographic lead system for use in patients with acute myocardial infarction Our studies indicate that it is possible to use a multiple lead system in acutely ill patients without any additional discomfort to the patients.

Method

We elected to use the orthogonal lead system devised by Frank [2] It is the most widely used vectorcardiographic lead system standard notation has been agreed upon and normal and abnormal values have been established Two commercially available monitoring cables (Becton Dickinson Co Rutherford N J) were altered. the head (H) and midback (M) electrodes of the Frank system are attached to one cable and the right (I) and left (A) axillary the anterior chest (E) and midchest (C) leads to the other cable (Fig 1) The right (RL) and left (LL) leg leads also are attached to the second cable the right leg signal is used as an isolated ground reference and the left leg signal is used to construct the Y signal In practice the right and left leg leads are placed on the lateral hip areas We place the chest and neck electrodes according to Frank with the exception that the transverse plane is located at the intersections of the fourth intercostal spaces

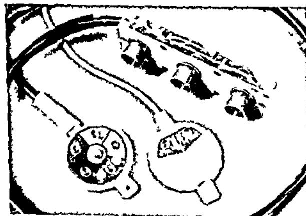


Fig 1 Monitoring cable modification used in the present investigation Two standard monitoring cables have been modified as described in the text They are joined to form two cables which enter the resistance network shown in the upper right

From the Myocardial Infarction Research Unit and Cardiology Unit, Department of Medicine University of Rochester Medical Center Rochester N Y 14642

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Reprint requests Dr Morrison Hodges Cardiology GG608 University of Rochester Medical Center Rochester N Y 14642

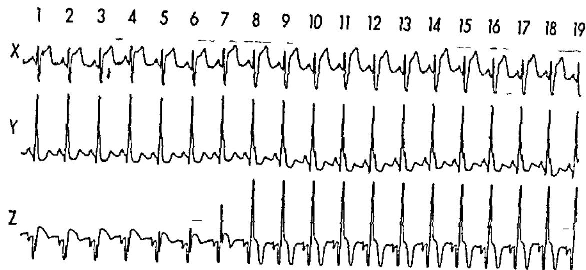


Fig 2 Frank X Y and Z leads recorded from a patient with a recent acute myocardial infarction Standardization = 2 5 mV full scale See text for explanation

and the parasternal lines as suggested by Langner and associates[3] for recumbent subjects Commercially available monitoring electrodes are used (Dispose El Becton Dickinson Corporation Rutherford N J), which have a low profile and are thus less likely to press firmly into the skin

The two cables are then joined to form a single cable which leads into a resistance circuit, enclosed in a plastic box (Fig 1) The resistance circuit is as described by Frank except that we chose 100 000 Ω as our constant so that three signals—the X Y and Z leads—form the electrical output These signals are then amplified by standard instrument amplifiers (Brush Clevite Cleveland Ohio) and displayed on a pressurized ink recorder and oscilloscope (Brush Clevite) (Fig 2)

For display purposes we have chosen to orient the leads so that the upper part of the tracings represent the patients left, inferior and anterior aspects in Leads X Y, and Z respectively (Fig 2)

Results

We have monitored the Frank vectorcardiogram in over 75 patients using the above approach Difficulties have been minimal In several patients who were very active in bed minor skin erosions have occurred at the H and M lead positions application of tincture of benzoin to the part of the skin in contact with the electrode has helped reduce this problem No patient has complained of excess wires or paraphernalia Baseline noise and movement has occurred in some patients particularly in Lead Y, but this has usually not obscured arrhythmia or QRS evaluation We routinely change the electrodes every 24 to 36 hours and shift the electrode position 1 cm or so, to avoid the skin erosion referred to above By keeping the electrode location within 1 cm of ideal location we have not noted any alteration or distortion of the basic X Y , and Z lead morphology In this fashion we have been able to monitor the Frank vectorcardiogram leads for periods up to 10 days without problems

In several patients we have obtained simultaneous Frank vectorcardiograms using our procedure as well as a commercially available vectorcardiogram machine (Model 1507A Hewlett Packard Corporation Palo Alto, Calif) The X , Y and Z-leads and vector loops appear very similar with the two techniques

Fig 2 shows the X Y and Z leads from a patient with a recent anterolateral myocardial infarction The diagnosis of an acute infarction can be inferred from the ST elevation present in Leads X and Z as well as the QS complex in Lead Z and the small Q wave in Lead X. Sinus rhythm can be appreciated in all three leads but a widening of the QRS complex begins with beat 5 and eventuates with a significant conduction defect which is present in the last 10 beats A specific diagnosis of the conduction defect (right bundle branch block) can be made from consideration of the orthogonal Frank leads Although careful scrutiny reveals the widened QRS in all three leads it is likely that the change would be detected on an oscilloscope screen only in Lead Z

In another patient we observed the onset of a left bundle branch block which was easily seen in Leads X and Y but not in Lead Z

Discussion

Monitoring of three orthogonal electrocardiographic leads offers several advantages over the monitoring of a single lead. First it allows diagnostic information to be available from the QRS complex. Second, it maximizes the opportunity for accurate rhythm analysis. It reduces the chances of a P wave or other information being buried in a single lead. Third it allows for calculation of spatial magnitude and direction of the electrocardiographic complex. We have recently utilized this feature to study the ST segment in patients with myocardial infarction.[4] This approach to monitoring should allow for more accurate and reliable monitoring of acutely ill patients.

Monitoring of patients with the approach we have described does present several problems. The equipment is obviously more complicated and expensive. Three channels of oscilloscopic display are required for each patient if the approach is to be maximally utilized. Also experience with vectorcardiographic interpretation is necessary in order to properly evaluate the QRS complex. We feel that additional information available in selected patients justifies further investigative use of this technique however.

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Conduction system examination in a case of spontaneous heart block in a dog

Saroja Bharati M D
Kenneth M Rosen M D
Robert A Miller M D
Maurice Lev M D *
Chicago Ill.

The dog is used extensively today as an experimental animal in electrophysiology It is therefore necessary to be familiar with the various arrhythmias which occur spontaneously in this animal

We had occasion to examine the heart of a dog who clinically showed complete heart block Comprehensive studies of the conduction system were done which comprise the basis for the present report

Clinical review

This was a 2 year old boxer who was well until one week prior to death At this time he was noted to be in heart failure and to have a pulse between 30 and 40 per minute Despite medical management the dog s condition deteriorated during the ensuing week He was referred to the medical center for pacemaker implantation

The dog was brought immediately to the cardiovascular laboratory Needle electrodes were placed in the four extremities and an electrocardiogram was obtained on an oscilloscopic photographic recorder (Electronics for Medicine DR 12) This revealed complete A V (atrioventricular) block with an atrial rate of 88 and a ventricular rate of 21 QRS complexes were narrow with left axis deviation suggesting a junctional escape rhythm (Fig 1) An electrode catheter was passed to the right heart in an unsuccessful attempt to record His bundle electrograms Upon entering the right atrium with the electrode catheter atrial flutter was induced (Figs 2, *A* and *B*) A V block persisted and the dog s heart rate progressively slowed during the procedure Ventricular fibrillation developed and the dog could not be resuscitated

Laboratory data showed a white blood count of 20 000 hemoglobin of 15 Gm and serum glutamic pyruvate transaminase of 40 units

Postmortem examination Post mortem examination was limited to the heart

Heart The heart weighed 118 grams Grossly the heart was normally formed The valves and coronary arteries were normal

Microscopic examination

Method The sinoatrial (SA) node was not available for study The approaches to the SA and A V nodes the A V node the A V bundle and bundle branches up to the level of the moderator band were serially sectioned and every tenth section was retained Alternate sections were stained with hematoxylin eosin and Weigert van Gieson stains In this manner 772 sections were examined This method of examination has previously been published [1]

Findings

ATRIAL SEPTUM The atrial septum was markedly infiltrated and replaced by fat tissue with very little muscle remaining The arterioles were thickened (Fig 3 *A*)

APPROACHES TO THE A V NODE These were almost

From the Congenital Heart Disease Research and Training Center Hektoen Institute for Medical Research the Departments of Pathology—Northwestern University Medical School Pritzker School of Medicine University of Chicago The Chicago Medical School University of Health Sciences and Loyola University Stritch School of Medicine *Departments of* Pathology and Medicine Abraham Lincoln School of Medicine University of Illinois and Pediatric Cardiology Department Cook County Children s Hospital Chicago

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Reprint requests Dr M Lev 637 S Wood St Chicago Ill. 60612

* Career Investigator and Educator Chicago Heart Association

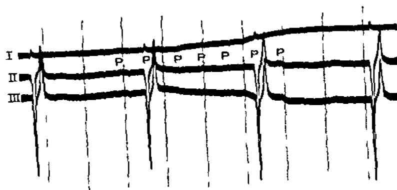


Fig 1 Electrocardiogram showing complete A V block with an atrial rate of 88 per minute and a ventricular rate of 21 per minute Note the narrow QRS escape rhythm with left axis deviation. Paper speed is 25 mm per second and the time lines are at one second

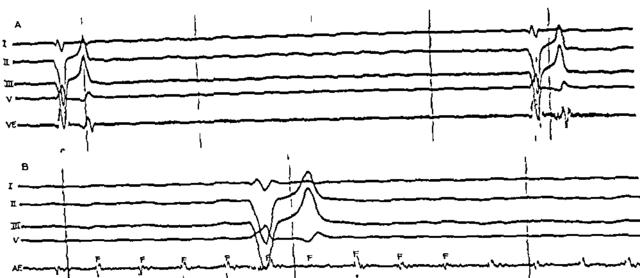


Fig 2 Bipolar intraventricular (Panel *A*) and intra atrial (Panel *B*) electrograms Note atrial flutter with complete A V block

completely replaced by fat (Fig 4) The arterioles were likewise thickened and narrowed (Fig 3 *B*)

A V NODE. Only a remnant of A V node was present which had practically no connection with atrial musculature (Fig 4) It likewise had only a tenuous connection with the bundle of His (Fig 5) Occasional hemorrhage was seen Some of the arterioles were thickened

A V BUNDLE, PENETRATING PORTION The parenchymal cells were irregularly stained and considerably vacuolated. There was moderate to marked replacement by fat tissue (Fig 6) Occasional arterioles were thickened (Fig 3 *C*)

A V BUNDLE, BRANCHING PORTION This was very short and showed fibrosis in the region of the junction with the left bundle branch in its posterior portion

BIFURCATION There was moderate to marked replacement by fat with irregular staining and vacuolization as above

LEFT BUNDLE BRANCH The posterior fibers of the main bundle given off before the bifurcation were replaced by fibroelastic tissue The fibers given off after the bifurcation showed moderate fibrosis and considerable acute degenerative changes In the periphery of the left bundle branch there was marked replacement by fat tissue more in the posterior radiation than in the anterior

RIGHT BUNDLE BRANCH This showed slight fibrosis with acute degeneration of cells as described



Fig 3 *A* approaches to A V node Three large arterioles moderately to markedly thickened. Weigert van Gieson stain ×45



Fig 3 *B* small arteriole on the periphery of A V node Hematoxylin and eosin stain ×375

above In the periphery there was marked fatty infiltration

VENTRICULAR SEPTUM Patchy fibrosis with small scars was present throughout with considerable arteriolosclerosis

Discussion

Spontaneous atrioventricular block in a dog is rare as are comprehensive studies of the conduction system when this arrhythmia occurs In a female setter of 6 to 7 years with ventricular septal defect, aortic insufficiency and presumed A V block, Lev Neuwelt and Necheles[2] found degenerative changes and fibrosis of the bundle of His and its branches accompanied by arteriolosclerosis with narrowing of the arterioles of the ventricular septum Andre[3] found only one instance of temporary complete heart block in a study of 24 dogs with enlargement of the heart with congestive heart failure Rapic and Sultic[4] reported Adams Stokes attacks during complete heart block in a 14 year old spaniel During other intervals there was regular sinus rhythm



Fig 3 *C* small arteriole on the periphery of bundle of His *Hematoxylin and eosin stain ×375 A = atrium* V = ventricle

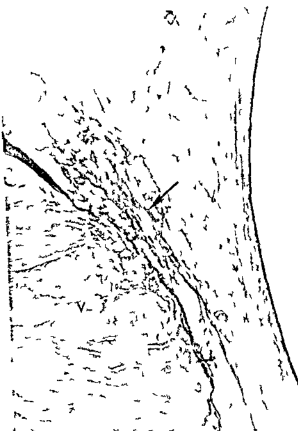


Fig 4 Remnant of A V node with no connection with the atrial musculature Weigert van Gieson stain × 45 V = ventricular myocardium Arrow points to A V node



Fig 5 Remnant of node forming bundle of His Weigert van Gieson stain, × 45 N = remnant of node B = beginning of bundle of His V = ventricular myocardium

Pathologically they described sclerosis of the coronary branches draining the conduction system and an atrophy of the proximal part of the A V node Patterson and co workers[5] in an extensive study of the occurrence of arrhythmias in dogs reported conduction disturbances in 95 out of 3 000 dogs. There were only two instances of atrioventricular block one transient and one permanent No autopsies were done on these dogs James and Drake[6] studied eleven Doberman pinschers 8 weeks to 10 years old, who died suddenly No electrocardiogram or examination of the heart beat or pulse rate were available except in one dog where the pulse was found to be absent shortly before death Histologically they found the identical cardiac lesions in ten dogs There was focal degeneration of the His bundle with almost complete replacement by fat This was associated with cartilage and bone formation in the adjacent central fibrous body The cause of these lesions was considered to be narrowing of the small coronary arteries supplying these structures James and Konde[7] described the conduction system in a case of heart block in a mongrel 1 year old dog The SA and A V nodes and the proximal part of the His bundle showed primitive cells At the same time there was a lack of communication between the A V node and the anterior and middle internodal pathways Denac Stunzi and Mehring[8] reported what is apparently a case of atrioventricular block with a ventricular escape rhythm in a two year old pinscher Histologically they found hypoplasia of the atrial parenchyma

Our case somewhat resembles that of Denac Stunzi and Mehring[8] and perhaps that of Rapic and Sutlic[4] and in part that of James and Konde[7] There is lack of communication between the atria and the A V node atrophy of latter structure disruption in its continuity with the atrioventricular bundle and degenerative changes in the entire conduction system Associated with these findings is arteriolar thickening with marked fat tissue replacement of the atria



Fig 6 Bundle of His at bifurcation showing fatty infiltration and acute degeneration Hematoxylin and eosin stain × 90 V = ventricular myocardium Arrows point to bundle

and fibrosis with small scars of the ventricles We are therefore dealing with block at the junctional area and this may be correlated with the narrow QRS

However, the basic type of heart disease present in this dog is not clear We may be dealing with arteriolosclerotic heart disease which is known to occur in dogs and the fatty infiltration replacement of the atria and their connections with the A V node and the atrophy of the A V node are the manifestations of an ischemic process On the other hand we may be dealing with a congenital lack of connection between the A V node and the atria, a cause of congenital A V block in man [9] In the latter however there is no arteriolosclerosis in the reported cases We therefore favor the conceptions of Rapic and Sutlic[4] and James and Drake[6] that we are dealing, in our case, with arteriolosclerotic heart disease and its effects upon the conduction system

Summary

This is a serial section study of the conduction system in a 2 year old boxer with electrocardiographic evidence of complete A V block The following findings were present a lack of communication between the atria and the A V node atrophy of the A V node and tenuous connections between the A V node and the A V bundle These were accompanied by acute degenerative changes in the conduction system These changes are considered to be the result of arteriolosclerotic heart disease

We wish to express our appreciation to Miss Mary L. Blazevich for her technical assistance and to Miss Florence Kotal for her assistance in the preparation of this paper

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Atrial response during ventricular fibrillation

Anthony N Damato M D
Sun H Lau M D
P Jacob Varghese M D
Gustavus A Bobb
Staten Island, N Y

The ventricular response during atrial fibrillation has been extensively studied and it is generally agreed that in atrial fibrillation concealment within the A V node is the major determinant of the frequency and irregularity of the ventricular response[1-9] In contrast studies dealing with the atrial response to ventricular fibrillation are almost nonexistent

It was the purpose of this investigation to study the electrical activity of the atria and bundle of His during induced ventricular fibrillation in the intact heart of dogs

Methods

Adult mongrel dogs (15 to 35 kilograms) were anesthetized with pentobarbital Na 30 mg per kilogram of body weight given intravenously The trachea was cannulated and the animals artificially respirated with room air Supplemental anesthesia was given as required A thoracotomy was performed at the fourth right intercostal space and the pericardium incised Close bipolar plunge wire electrodes were inserted into the regions of the sinus node (SN) Bachmann s bundle (BB) the right atrial appendage (RAA) left atrial appendage (LAA) and the coronary sinus (CS)[10] Two sets of close bipolar wire electrodes were inserted into the region of the bundle of His[11] One set of wires was used to pace the bundle of His and the other set to record His bundle activity Close bipolar wires were also inserted into the free wall of the right ventricle for ventricular pacing The left cervical vagus nerve was isolated and sectioned and the distal end impaled with close bipolar stimulating wires Electrocardiographic Leads II was recorded along with multiple atrial electrograms and the bundle of His

Electrical stimulation of the bundle of His or right ventricle was accomplished using a programmed digital stimulator which delivered rectangular pulses of 1 5 msec duration at twice diastolic threshold Vagal stimulation was accomplished using a Grass stimulator which delivered 2 msec impulses at a frequency of 40 per second and at a voltage of 15 Multiple atrial and bundle of His electrograms were recorded at 40 to 500 Hz All tracings were taken on a multichannel oscillographic photographic recorder at paper speeds of 150 mm per second Recordings were taken during sinus rhythm bundle of His pacing right ventricular pacing and ventricular fibrillation

Ventricular fibrillation was induced by delivering a 1 to 3 second burst of repetitive stimuli (40 per second) to the free wall of the right ventricle

Validation of the His deflection Validation of the antegrade His deflection (H) was accomplished by pacing the bundle of His and noting that (1) the interval from the stimulus artifact (S) to the onset of ventricular depolarization (V) i e the S V interval was the same as the H V interval during sinus rhythm and (2) that the resultant QRS complexes were the same[10,11]

Validation of the retrograde His deflection was

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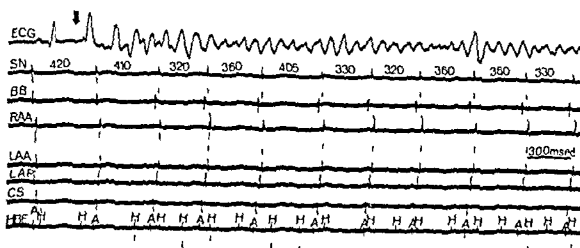


Fig 1 The tracings from top to bottom are ECG (Lead II) close bipolar electrogram from the region of the sinus node (SN) Bachmann s bundle (BB) right atrial appendage (RAA) left atrial appendage (LAA) the posterior left atrium (LAP) and the coronary sinus (CS) HBE is the His bundle electrogram recording showing a low atrial septal electrogram (A) and a His deflection (H) The above abbreviations will be used throughout the text unless otherwise stated The arrow designates the point at which ventricular stimulation was initiated in order to induce ventricular fibrillation. Note the sequence of atrial electrogram recordings for the sinus beat (first beat) The second atrial beat represents fusion activation and thereafter the atria are retrogradely depolarized characterized by early activation of the low atrial septal electrogram (A) Bachmann s bundle (BB) and the coronary sinus (CS) The atrial cycle length in milliseconds is shown on the SN electrogram recording

accomplished by noting that when the right ventricle was paced at a rate sufficient to produce 1 1 retrograde conduction the interval from the retrograde His deflection to the onset of the low atrial electrogram (H A interval) was the same as the interval between the stimulus artifact and the retrograde atrial electrogram (S A interval) when the bundle of His was paced at comparable rates [10] In all cases during retrograde activation of the bundle of His the polarity of the H deflection was changed from that of antegrade activation

Also upon completion of the studies the hearts were removed, and the location of the recording and stimulating electrodes was confirmed by exposing the intact bundle of His according to the dissection technique of Elizzari and associates [12]

Results

Ventricular fibrillation studies were performed on a total of 23 nonconsecutive animal studies The decision to perform ventricular fibrillation studies was based entirely upon the type of His bundle recording obtained Ideal recordings were those in which the plunge wires yielded predominately a His deflection with little or no ventricular activity or a His deflection with only atrial activity When the plunge wires recorded a His potential with a significant amount of ventricular activity, the latter made identification of a retrograde His deflection during ventricular fibrillation more difficult, although not impossible

Prior to the induction of ventricular fibrillation the capacity to retrogradely conduct across the A V node was tested in each animal by pacing the right ventricle at cycle lengths between 400 and 200 msec Fourteen animals demonstrated consistent 1 1 retrograde conduction at various paced cycle lengths (Group A) in four animals (Group B) retrograde conduction was intermittent and in three animals (Group C) no retrograde conduction was observed at any paced cycle length Retrograde conduction across the A V node was also absent in two animals (Group D) with antegrade A V block within the His Purkinje system

The following are the results obtained during the first five minutes of continuous ventricular fibrillation The most common conduction pattern noted at the very onset of ventricular fibrillation was that of rapid irregular retrograde activation of the bundle of His and atria This type of response was observed in all 14 animals of Group A and four animals of Group B Fig 1 is representative of these findings The first beat is

Fig 2 Same animal experiment as shown in Fig 1 Recordings were made after one minute of continuous ventricular fibrillation and show the spontaneous transition from complete retrograde activation of the atria (first two atrial beats) to fusion activation of the atria (beats 3 to 6) to complete sinus activation thereafter For beats 3 to 6 fusion activation of the atria is judged to be present because of the altered sequence *of the CS electrogram* (compare with the first atrial beat of Fig 1) and also because the interval between the CS electrograms does not become 390 msec until the seventh atrial beat

Fig 3 Validation of the retrograde *His deflection* during ventricular fibrillation The bundle of His was stimulated (S) at a cycle length of 150 msec which prevented its retrograde activation by the fibrillating ventricles The atria are antegradely activated with the SN *electrogram* preceding all other atrial recordings Note the absence of spontaneously occurring His deflections

of sinus origin The sinus cycle length was approximately 420 msec Note that the antegrade His potential is an upright deflection Rapid ventricular stimulation in order to produce ventricular fibrillation begins at *the arrow* The second QRS complex is a stimulated ventricular beat in which a retrograde His deflection (opposite polarity) occurs after the onset of ventricular depolarization The second atrial impulse represents fusion activation of the atria with the low atrial and coronary sinus electrograms activated earlier than in sinus beats During the subsequent ventricular fibrillation the bundle of His was irregularly rapidly and retrogradely activated The atria were also retrogradely activated at an irregular cycle length and at a frequency less than that of the bundle of His

Fig 2 (same experiment as Fig 1) was recorded *after* one minute of continuous ventricular fibrillation and shows the transition from retrograde atrial activation to sinus activation at a cycle length of 390 msec The bundle of His continued to be irregularly activated in a retrograde fashion

In Fig 3 validation of the bundle of His was obtained *during the* course of ventricular fibrilla

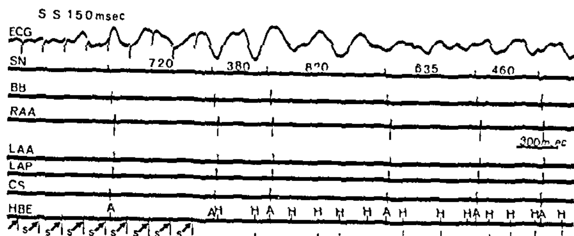


Fig 4 Same experiment as Fig 3 Upon termination of His bundle stimulation the retrogradely activated His bundle deflections reappear The atrial cycle length just prior to and following termination of bundle of His stimulation became irregular

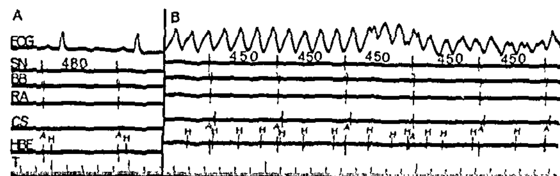


Fig 5 Continuous sinus activation of the atria during ventricular fibrillation Panel *A* shows two sinus beats at a cycle length of 480 msec Panel *B* was recorded immediately after the onset of ventricular fibrillation and shows continuous sinus activation of the atria at a cycle length of 450 msec Irregular retrograde activation of the His bundle occurs with retrograde block. *T* represents time lines at 10 and 100 msec intervals

tion The bundle of His was stimulated at a cycle length of 150 msec Note the absence of spontaneous His bundle activity and that the atria continue to be antegradely activated

Fig 4 was recorded after four minutes of continuous ventricular fibrillation The atria were antegradely activated but at a more irregular rate Following cessation of His bundle pacing spontaneous retrograde activation of the bundle of His resumes

In all three animals of Group C the atria continued to be activated by the sinus node throughout the five minute period of ventricular fibrillation The irregularly occurring His bundle impulses were retrogradely blocked within the A V node as illustrated in Fig 5

In four studies ventricular fibrillation was associated with distinct periods of retrograde A V nodal Wenckebach cycles In two additional studies retrograde A V nodal Wenckebach periods with re entry were observed

Fig 6 with its accompanying ladder diagram illustrates an ordinary 3 2 retrograde A V nodal Wenckebach cycle followed by a retrograde A V nodal Wenckebach cycle which was terminated by re entry in which the eighth His deflection was antegradely depolarized The irregular H H intervals are compatible with an exit Wenckebach cycle of a low junctional or subjunctional pacemaker

In two animals (Group D) complete A V dissociation resulted when the wires were plunged into the region of the common bundle Panel *A* of Fig 7 shows complete A V dissociation in which the A H interval of the nonconducted atrial impulses was constant at 66 msec and the ventri

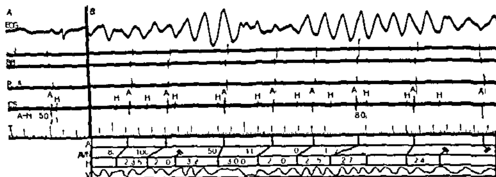


Fig 6 Retrograde A V nodal Wenckebach cycles with and without re entry Panel *A* depicts a single sinus beat with antegrade activation of the atria and bundle of His Panel *B* represents ventricular fibrillation with retrograde activation of th atria Electrical activity of the atria (A) A V node (AVN) bundle of His (H) and ventricles (V) is illustrated in the ladder diagram at the bottom of the graph Retrograde A V nodal conduction times and H H intervals are given in milliseconds Two consecutive retrograde A V nodal Wenckebach cycles oc cur In the first a 3 2 retrograde sequence is terminated by an impulse which is blocked in the A V node The second Wenckebach cycle is a 4 3 sequence A retrograde A V nodal conduction time of 190 msec was associated with re entry within the A V node and terminated by antegrade activation of the bundle of His (eighth His deflection) In the ladder diagram re-entry is depicted as a broken bar line

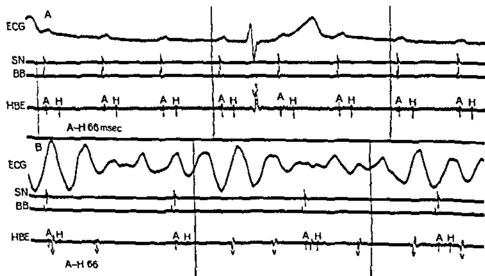


Fig 7 Panel *A* shows complete A V dissociation. An ectopic atrial pacemaker located in or near Bachmann s bundle controlled the atria. Each atrial impuls was blocked within the His Purkinje system and an idio ventricular pacemaker controls the ventricles The A H interval of the nonconducted atrial impulse is 66 msec During ventricular fibrillation (Panel *B*) the atrial impulses continue to be blocked within the His Purkinje system and the A H interval remains at 66 msec

cles were controlled by an idioventricular pace maker In Panel *B* the atria and bundle of His continued to be antegradely activated during ventricular fibrillation Retrograde impulses from the fibrillating ventricle were blocked in the Purkinje bundle branch system.

In all ventricular fibrillation studies retro grade conduction across the A V node could be abolished by vagal stimulation Fig 8 is represen tative of these findings Upon termination of vagal stimulation retrograde A V nodal conduc tion resumed Occasionally the atria were acti vated by the sinus node immediately after re lease of vagal stimulation and later retrogradely

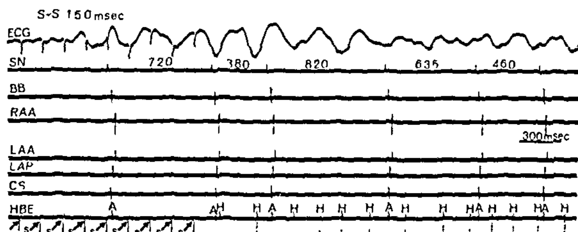


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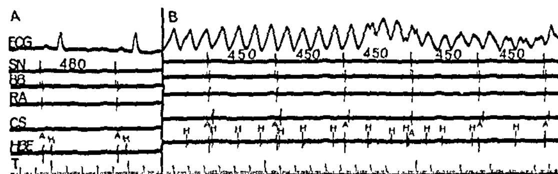


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In two animals (Group D) complete A V dissociation resulted when the wires were plunged into the region of the common bundle Panel *A* of Fig 7 shows complete A V dissociation in which the A H interval of the nonconducted atrial impulses was constant at 66 msec and the ventri

ventricular interval sequences in atrial fibrillation[2,3,7,8] In some instances these patterned ventricular sequences can be attributed to extraneous pacemakers controlling the ventricles However in the absence of extraneous pacemakers the mechanisms for the patterned ventricular sequences during atrial fibrillation are less clear In the present study patterned atrial interval responses during ventricular fibrillation were also noted At times these were due to sinus node capture of the atria (so called extraneous pacemaker) At other times the patterned sequences were due to retrograde A V nodal Wenckebach periodicity

Of interest was the fact that for relatively long periods of time both the sino-atrial and atrioventricular nodes were responsive to the influence of vagal stimulation In the fibrillating heart vagal stimulation resulted in block of retrograde A V nodal conduction and sinus arrest Vagal stimulation did not alter the frequency of retrograde His bundle depolarizations which is in support of previous observations that vagal stimulation does not alter either antegrade or retrograde conduction in the His Purkinje system[13]

Summary

Electrical activity of the bundle of His and atria were recorded during sinus rhythm and electrically induced ventricular fibrillation in 23 dogs Multiple bipolar atrial electrograms obtained from several sites within the right and left atria permitted the determination of the frequency regularity and sequence of atrial activation (i e sinus or retrograde) during ventricular fibrillation Prior to the induction of ventricular fibrillation the capacity to retrogradely conduct across the A V node was tested in each animal by pacing the right ventricle at various cycle lengths Fourteen animals demonstrated consistent 1 1 retrograde conduction at various paced cycle lengths (Group A) in four animals (Group B) retrograde conduction was intermittent and in three animals (Group C) no retrograde conduction was observed at any paced cycle length Ventriculo atrial conduction was also absent in two animals (Group D) with antegrade A V block within the His Purkinje system.

The most common conduction pattern noted at the onset of ventricular fibrillation was that of rapid, irregular retrograde activation of both the bundle of His and atria However the frequency of retrograde activation of the atria was less than that of the bundle of His indicating that the A V node was a site of retrograde concealment of impulses This conduction pattern was noted in all animals of Groups A and B In all animals of Groups C and D the atria continued to be activated in a sinus sequence during ventricular fibrillation In Group C animals the A V node was the site of both antegrade and retrograde concealment In the two animals with A V block (Group D) the site of retrograde concealment was distal to the site of block

In six studies retrograde A V nodal Wenckebach cycles with and without re entry were observed for varying periods of time

Less often the irregular atrial responses during ventricular fibrillation were accounted for by short periods of sinus capture interspersed with periods of retrograde capture

During ventricular fibrillation retrograde conduction across the A V node could be abolished by vagal stimulation

The results of this study indicate that retrograde concealed conduction within the A V node is the major determinant of an irregular atrial response during ventricular fibrillation just as antegrade concealed conduction is the major determinant of an irregular ventricular response during atrial fibrillation

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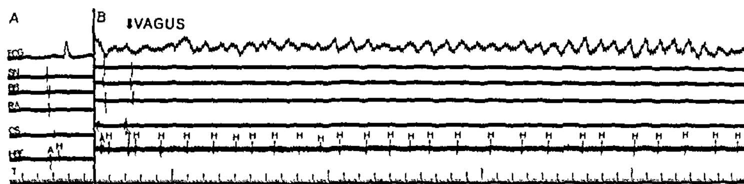


Fig 8 Panel *A* is a sinus beat Panel *B* was recorded during sustained ventricular fibrillation The first part of this panel shows two retrograde atrial depolarizations With the application of vagal stimulation (arrow) retrograde block at the A V node occurred. Atrial activity ceased and the bundle of His continued to be retrogradely and irregularly activated

activated The effect of vagal stimulation on A V nodal conduction could be demonstrated for up to seven minutes following the onset of continuous ventricular fibrillation

During ventricular fibrillation electrical depolarization of the atria, as described above was associated with visible atrial contractions After about 10 seconds of continuous ventricular fibrillation the atria began to distend and eventually became three to four times their normal size Atrial contractions continued but were less prominent during atrial distention If the atria were decompressed by aspirating blood, atrial contractions appeared normal

In no instance did atrial fibrillation occur spontaneously during ventricular fibrillation In three instances of continuous ventricular fibrillation atrial fibrillation did occur during vagal stimulation

Discussion

The results of this study demonstrate that during ventricular fibrillation the A V node was a zone of retrograde concealment of impulses just as it is a zone of antegrade concealment during atrial fibrillation Retrograde concealment during ventricular fibrillation was evident from the fact that the number of retrograde His deflections exceeded the number of retrograde atrial depolarizations It is not known from the results of this study whether retrograde concealment also occurred within other areas of the His Purkinje system During ventricular fibrillation many impulses undoubtedly enter the distal Purkinje network but not all are retrogradely propagated to the bundle of His Retrograde block may occur at the muscle Purkinje junction or anywhere along the bundle branch system In a similar way, during atrial fibrillation many of the chaotic and rapid atrial impulses do not enter the A V node Block may occur within the atrium or at the atrio nodal junction

The fact that retrograde A V nodal concealed conduction occurred immediately with the onset of ventricular fibrillation indicates that ischemia of the A V node consequent to a decrease or absence of coronary blood flow did not play a major role in the nodal conduction pattern early in the course of ventricular fibrillation Thus in ventricular fibrillation the major determinant of an irregular atrial response is retrograde concealed conduction just as antegrade concealed conduction is the major determinant of the irregular ventricular response in atrial fibrillation Less often the irregular atrial responses during ventricular fibrillation were accounted for by short periods of sinus capture interspersed with periods of retrograde capture The ability of the sinus node to intermittently capture the atria was most likely due to an enhancement of its firing rate by a reflex increase in sympathetic tone as a consequence of the fall in blood pressure during ventricular fibrillation and/or stretch of the atria However, since an increase in sympathetic tone also enhances retrograde A V nodal conduction rapid retrograde depolarization of the atria prevented these accelerating mechanisms from capturing the atria as often as one might expect Sinus acceleration was evident when retrograde conduction across the A V node did not occur as shown in Fig 5

Several investigators have noted patterned

Direct myocardial effects of precatheterization medications

S L Faulkner M D
R C Boerth M D Ph D
T P Graham Jr M D
Nashville Tenn.

Medications given before cardiac catheterization in children should result in a well sedated but cooperative child and have no cardiorespiratory depressant effects Furthermore hemodynamic determinations made during the study should not be influenced by the specific type of premedication A combination of meperidine chlorpromazine and promethazine has been utilized widely for precatheterization sedation in children[1] In our experience this drug combination has not achieved adequate sedation in approximately one half of the children older than two years of age and additional medication given intravenously during cardiac catheterization has been required Furthermore alterations in systemic and pulmonary vascular resistance[2] as well as circulatory depression[3] with the meperidine chlorpromazine promethazine combination have been documented.

Recently we have reviewed our clinical experience with Innovar for sedation and analgesia during cardiac catheterization[4] Satisfactory sedation with absence of significant respiratory or cardiovascular depression was obtained with intramuscular Innovar (0 25 c c per kilogram) in children over two years of age For children less than two years of age a combination of meperidine (1 mg per kilogram) and hydroxyzine (1 mg per kilogram has been utilized before catheterization and supplemental intravenous meperidine (1 mg per kilogram) is given during the procedure as necessary Little information is available about the direct myocardial effects of these drugs It was the purpose of this investigation to determine the direct effects of these agents on myocardial contractility utilizing isometrically contracting isolated rabbit papillary muscle preparations and to compare these data with responses in isolated human atrial tissue under similar experimental conditions

Methods

Right ventricular papillary muscles were obtained from 32 adult New Zealand white rabbits killed by cervical fracture Right atrial strips from patients undergoing cardiac surgery were obtained from the amputated right atrial appendage before cardiopulmonary bypass (Table I) These atrial strips are routinely excised and discarded as part of the operative procedure The muscles were suspended by a light weight jeweler s chain from an isometric force transducer (Statham Model UC2) and the lower end of each preparation was secured by a stainless steel clamp The muscles were bathed in oxygenated Krebs bicarbonate solution maintained at pH 7 4 Papillary muscle preparations were maintained at a bath temperature of 30 C and human atrial strips at a temperature of 37 C Each muscle was stimulated with a 3 msec square wave pulse at a voltage 10 per cent above threshold through paired point electrodes placed just above the basal clamp Papillary muscles were stimulated at 24 beats per minute and atria at 60 beats per minute A stimulus artifact and isometric force were recorded on a direct writing oscillograph (Brush Mark 200) at a paper speed of 50 or 100 mm per second. The rate of isometric force development (dF/dt) was calculated

From the Division of Pediatric Cardiology and the Department of Surgery Vanderbilt University Hospitals, Nashville Tenn 37203

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Table I

Patient No	Age	Diagnosis
1	19 yrs	Tetralogy of Fallot
2	11 yrs	Valvular aortic stenosis
3	4 yrs.	Atrial septal defect
4	32 yrs	Tetralogy of Fallot
5	7 yrs.	Subvalvular aortic stenosis
6	5 mos	Ventricular septal defect

Table II Muscle bath concentrations producing 10 per cent decrease in developed stress and dS/dt in rabbit papillary muscle

	Concentration producing	
Drug	10 per cent decrease S (μg/mL)	10 per cent decrease dS/dt (μg/mL)
Innovar	0 4	0 8
Droperidol	3 0	6 3
Meperidine	45	52
Hydroxyzine	13	14
Meperidine hydroxyzine	18	20

S = str ss (Gm./mm ²)
dS/dt = maxim l rate f h nge of t ss (Gm./mm.²/sec)
I n ar = a c mbination f droperid l and f ntanyl in a 50 1 rat o
The dose f Inn ar gi en s that of the droperidol c mponent.

dt Both droperidol and Innovar produced small dose dependent decreases in time to peak stress development (Fig 3)

Meperidine hydroxyzine and the 1 1 combination of the two drugs produced dose dependent decreases in S dS/dt and time to peak stress development (Figs 4 through 6) The dose response curves for the meperidine hydroxyzine combination were not significantly different from the curves for hydroxyzine alone At any given concentration hydroxyzine had greater negative inotropic effects than meperidine

Man Dose response curves of human atrial tissue to Innovar (Patients 1 2 and 3 Fig 7) were similar to the mean dose response curve in rabbit papillary muscles As with the animal data no positive inotropic effects were noted and there was a very steep slope to the descending limb of the curve The concentration of Innovar producing a 10 per cent decrease in dF/dt was 1 0 μg per milliliter for the human atria versus 0 80

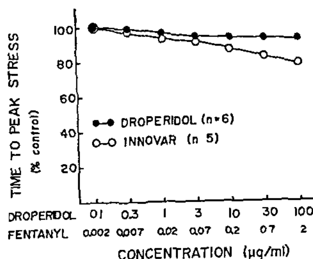


Fig 3 Mean dose response curves in rabbit papillary muscles showing the effects of increasing concentrations of Innovar and droperidol on time to peak stress development The concentration of Innovar for each response is the combination of the amounts of droperidol and fentanyl shown on the abscissa N = number of papillary muscles for each drug or drug combination

μg per milliliter for rabbit papillary muscle The dose response curves of strips from Patients 4 5 and 6 to the 1 1 combination of meperidine hydroxyzine were also very similar to that in rabbit papillary muscles (Fig 8) The concentration of the 1 1 meperidine hydroxyzine combination producing a 10% reduction in dF/dt was 20 μg per milliliter of each drug for rabbit papillary muscles and 11 μg per milliliter for human atrial strips

Discussion

The results of the present investigation demonstrate direct negative inotropic effects on rabbit papillary muscles for both droperidol and Innovar Fentanyl on the other hand, produced no inotropic effects on the papillary muscles in the dose range studied. The data from the human atrial strips indicate that Innovar exerts a comparable negative inotropic effect in man Previous studies in man[4, 5] and experimental animals[6, 7] have demonstrated minimal or no changes in cardiac function produced by Innovar or droperidol Whereas fentanyl has not been shown to produce any direct effects on the cardiovascular system in man[8] a dose related negative inotropic action has been demonstrated in isolated right ventricular papillary muscles from cats[9] and left ventricular trabeculae carneae of

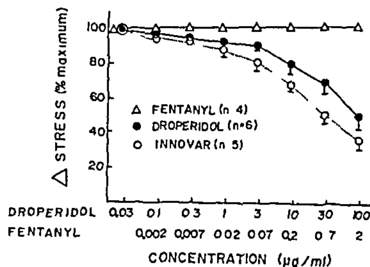


Fig 1 Dose response curves in rabbit papillary muscles showing the effects of increasing concentrations of Innovar droperidol and fentanyl as changes in peak developed stress Each symbol represents the mean value and the standard errors of the means are shown as brackets The concentration of Innovar for each response is the combination of the amounts of droperidol and fentanyl shown on the abscissa N = number of papillary muscles for each drug or drug combination

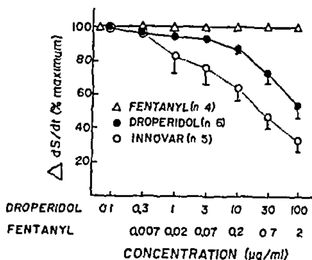


Fig 2 Dose response curves in rabbit papillary muscles showing the effects of increasing concentrations of Innovar droperidol and fentanyl as changes in the maximum rate of stress development (dS/dt) Each symbol represents the mean value and the standard errors of the means are shown as brackets. The concentration of Innovar for each response is the combination of the amounts of droperidol and fentanyl shown on the abscissa N = number of papillary muscles for each drug or drug combination

from a tangent drawn at the maximum upstroke of the isometric force tracing The time to peak force was determined as the time from the onset of contraction to the point of peak force

The mean cross sectional area for the rabbit papillary muscles was 0 70 ± 0 15 mm ² (mean ± standard error of the mean) The weight of the human atrial strips was 75 ± 20 milligrams Resting force for the papillary muscles varied from 0 15 to 0 7 gram and for atrial tissue from 0 5 to 1 0 gram

Each papillary muscle or atrial muscle strip was stretched until developed force was maximal and a 45 minute period was allowed before the experimental manipulation was begun Incremental doses of Innovar (a combination of droperidol 2 5 mg per cubic centimeter and fentanyl 0 05 mg per cubic centimeter or a drug ratio of 50 1, McNeil Laboratories, Inc) droperidol, fentanyl meperidine, hydroxyzine or a 1 1 combination of meperidine and hydroxyzine were added to the papillary muscle bath to produce cumulative dose response curves Only one drug was utilized in any muscle preparation High speed oscillographic tracings for each drug dosage were obtained when developed force was unchanged for five minutes Dose response curves for Innovar and the meperidine hydroxyzine combination were also obtained in the human atrial muscle preparations

For comparison of the responses of the muscle preparations to various drugs the control developed force (F) for atrial muscle strips or control developed stress (S force per unit cross sectional area) for papillary muscles and the control maximal rate of development of force or stress (dF/dt dS/dt) were assigned values of 100 per cent Similarly the time required to reach peak force in the control tracing was assigned a value of 100 per cent All results for each preparation were then expressed as a percentage of control Group responses were expressed as the mean response (± the standard error of the mean) for each dose

Results

Animal With respect to both developed stress and dS/dt Innovar and droperidol produced negative inotropic effects in the rabbit papillary muscle preparations (Figs 1 and 2) However the dose response curve to Innovar was shifted to the left compared to the curve for droperidol alone The concentration of each drug that would produce a 10 per cent decrease in developed stress or dS/dt is listed in Table II Fentanyl in the concentration range found in the doses of Innovar studied had no effect on developed stress or dS/

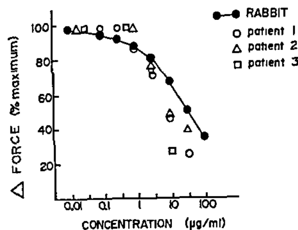


Fig 7 Dose response curves in atrial strips from three patients showing the effects of increasing concentrations of Innovar as changes in peak developed force The mean dose response curve for Innovar in rabbit papillary muscles is shown for comparison The concentrations of Innovar on the abscissa are expressed as the amount of droperidol in the Innovar drug combination

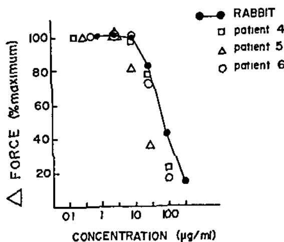


Fig 8 Dose response curves in atrial strips from three patients showing the effects of increasing concentrations of a 1 1 combination of meperidine and hydroxyzine as changes in peak developed force The mean dose response curve for this drug combination in rabbit papillary muscles is shown for comparison The concentrations shown on the abscissa are the concentrations of both the meperidine and hydroxyzine in the drug combination

concentration of 14 μg per milliliter for hydroxyzine and 52 μg per milliliter for meperidine The effect of the 1 1 combination of meperidine and hydroxyzine in the isolated muscle bath reflects mainly the negative inotropic effects of hydroxyzine (Fig 4 and 5) No direct effects of meperidine on myocardial contractility have been found in man [12] When meperidine is given intravenously to dogs (1 to 2 mg per kilogram) a transient decrease in cardiac output secondary to both a decrease in stroke volume and heart rate has been demonstrated.[13] Hydroxyzine (in doses of 1 2 to 20 mg per kilogram) in the intact animal appears to have no direct myocardial effect [14] The negative inotropic effects of hydroxyzine[14] and meperidine[9] on isolated cat papillary muscles compare qualitatively with our results although the cat would appear slightly more sensitive to these agents Similar observations have been made in cat and rabbit papillary muscles in our laboratory with respect to the negative inotropic effect of droperidol

Meperidine serum levels have been reported following both intravenous and intramuscular administration Fifteen to thirty minutes following intravenous meperidine injection (1 5 to 2 0 mg per kilogram) in man peak serum levels of 0 9 to 1 6 μg per milliliter have been recorded.[15] Following intramuscular administration of 0 44 to 1 0 mg per kilogram of meperidine to human volunteer subjects serum concentrations averaged 0 67 to 0 65 μg per milliliter at one and two hours respectively[16] similar levels have been found in children in our laboratory 10 minutes following administration of 1 mg per kilogram of intravenous meperidine Blood levels of hydroxyzine in man following oral or intramuscular administration have not been reported. With meperidine alone a 10 per cent reduction in dS/dt of rabbit papillary muscles occur at bath concentrations of 52 μg per milliliter Therefore approximately a one hundred fold safety range for direct myocardial depression in man exists for meperidine at a dose of 1 0 mg per kilogram

Correlation of serum concentration of any drug with hemodynamic results requires information regarding absorption rate of uptake in tissues speed of onset of action metabolic degradation and excretion of that drug Thus extrapolation of dose related responses in the isolated muscle bath to measured hemodynamic changes in the intact animal or man must be made with caution This investigation demonstrates that several precatheterization medications produce quantitatively similar depression of contractility in rabbit and human myocardium However because of the wide range of safety which is apparent between expected peak serum concentrations and the concentrations producing negative inotropic effects no direct de

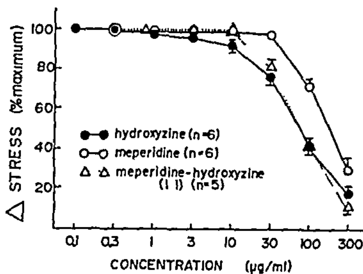


Fig 4 Dose response curves in rabbit papillary muscles showing the effects of increasing concentrations of meperidine hydroxyzine and a 1 1 combination of meperidine and hydroxyzine as *changes in peak developed stress* Each symbol represents the mean value and the standard errors of the means are shown as brackets N = number of papillary muscles for each drug or drug combination

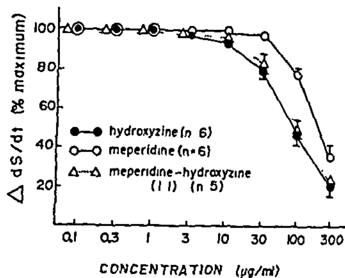


Fig 5 Dose response curves in rabbit papillary muscles showing the effects of increasing concentrations of meperidine hydroxyzine and a 1 1 combination of meperidine and hydroxyzine as changes in the maximum rate of stress development (dS/dt) Each symbol represents the mean value and the standard errors of the means are shown as brackets. N = number of papillary muscles for each drug or drug combination

rats [10] The concentrations of fentanyl required to produce this myocardial depression were approximately one thousand fold higher than the maximal concentration used in this study In the current investigation the negative inotropic effects of Innovar were greater than that of droperidol *at any given concentration of droperidol* This observation raises the possibility that fentanyl may have a synergistic effect with droperidol in depressing the inotropic state since fentanyl alone produced no change in either developed stress or dS/dt

Available information on serum levels of droperidol following either intravenous or intramuscular injections indicate a maximum plasma concentration of 0 08 µg per milliliter following a dose of 0 066 mg per kilogram [11] This dose (0 0625 mg per kilogram) is similar to that used by us before cardiac catheterization If one assumes that this amount of drug rapidly distributes in the extracellular water volume, then theoretical peak plasms levels would be approximately 0 08 µg per milliliter The concentration of droperidol (when combined with fentanyl in Innovar) producing a 10 per cent reduction in dS/dt in the rabbit papillary muscle is 0 8 µg per milliliter and in human atria 1 0 µg per milliliter Thus, it would appear there should be no direct depression of myocardial contractility in man following clinical usage of Innovar or droperidol (0 0625 mg per kilogram) since there is at least a

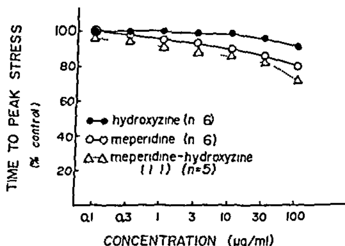


Fig 6 Mean dose response curves in rabbit papillary muscles showing the effects of increasing concentrations of meperidine hydroxyzine and a 1 1 combination of meperidine and hydroxyzine on time to peak stress development N = number of papillary muscles for each drug or drug combination

10 fold difference between peak measured plasma concentrations and the concentrations required to produce a 10 per cent decrease in dS/dt

This investigation demonstrated dose related negative inotropic effects of meperidine hydroxyzine and a 1 1 combination of meperidine hydroxyzine in both rabbit papillary muscles and human atrial tissue Ten per cent depression in dS/dt of rabbit papillary muscles occurs at a bath

Echocardiographic features of experimental left atrial tumor

Monty M Bodenheimer M D
Howard L Moscovitz, M D
John Pantazopoulous M D
Ephraim Donoso M D
New York N Y

The relative rarity of atrial tumors[1,2] and their highly variable clinical manifestations[3] have resulted in frequent misdiagnosis and these tumors are often unsuspected or difficult to diagnose and confirm Although echocardiography has greatly enhanced the diagnosis of left atrial tumors[4-10] its accuracy has been questioned and the possibility of false positive diagnosis in the presence of left atrial thrombus or mitral valve disease has been raised.[11] A model was devised involving the introduction of a distensible balloon into the left atrium of a dog a procedure simulating a prolapsing left atrial tumor The echocardiographic features of this simulated tumor and mitral valve function in its presence were then assessed

Methods

Ten adult mongrel dogs averaging 15 kilograms were anesthetized with intravenous sodium pentobarbital A left thoracotomy was performed and a small balloon was then introduced into the left atrium and its narrow neck sutured to the left atrial appendage The distensible stalk permitted the inflated balloon to enter the left ventricle during ventricular diastole and return to the left atrium in systole The balloon was inflated with variable volumes of air or indocyanine green solution and thus simulated atrial tumors of various sizes Coupled electrical pacing employing an Flecath catheter was used in some studies to slow the heart rate

All echocardiograms were recorded by means of a Unirad Series C ultrasonoscope with a repetition rate of 1 000 per second and a frequency of 2 0 mHz The transducer utilized a 10 mm crystal All photographs were recorded on Polaroid film at a sweep speed of 25 or 50 mm per second from a Unirad Model 175 variable storage monitor

The heart was lifted slightly in a pericardial sling to bring the interventricular septum into view The transducer was then applied directly to the myocardium on the right ventricular side of the septum and angled to detect the balloon in either the left atrium or the left ventricle as well as behind the anterior mitral leaflet. Localization of the septum could be made easily by noting the transducer s position on the heart As all structures were located very close to the transducer the gain and reject were adjusted to limit the echoes from the near field However the time gain control was set to balance all echoes beyond the point of the septal surface A simultaneous electrocardiogram was recorded

Utilizing either air or indocyanine green to fill the balloon resulted in equally distinct echocardiograms and permitted exact localization of the balloon as well as its relationship to the left heart structures.

Results

E to F slope The normal E to F slope was unchanged slowed or reversed depending upon tumor size In Fig 1 even though a definite tumor is present no reduction in the E-to F slope occurred (EF = 122 mm per second) However with the larger tumor of Fig 2 the E to F slope is reversed (EF = −3 mm per second) and tumor prolapse occurred earlier in diastole

Tumor mobility Fig 3 demonstrates how

From the D vision f Cardiology Departme t of Medic ne Mount S nai Hosp tal, New Yo k.

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Repr t requests Dr Monty M. Bodenheime 1831 F rrington Rd. Philadelphia, Pa. 19151

pression of contractility in man should be expected following clinical doses of these agents.

Summary

The direct effects of droperidol, fentanyl, Innovar, meperidine, hydroxyzine and a 1 1 combination of meperidine and hydroxyzine on myocardial contractility were determined utilizing isometrically contracting rabbit right ventricular papillary muscles and human atrial strips In rabbit papillary muscles, no positive inotropic effects were found for any of these drugs, but each drug except fentanyl produced a dose dependent decrease in developed stress, dS/dt and time required to reach peak stress Isolated human atrial strips responded to Innovar and the 1 1 combination of meperidine and hydroxyzine in a manner quantitatively similar to that in the rabbit papillary muscle At concentrations of these drugs in the muscle bath comparable to measured peak serum levels in man, no change in myocardial contractility was observed

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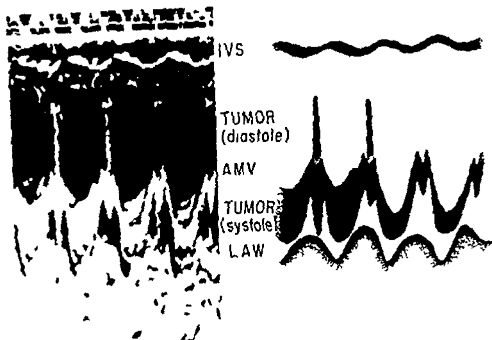


Fig 3 Tumor motion is seen in both systole and diastole in the first two beats After deflation (beat three) the tumor is absent

was a variable delay from the time of opening of the mitral valve to the time that the tumor prolapsed into the left ventricle With lesser degrees of balloon inflation (Fig 1) prolapse occurred late in ventricular diastole This was a consistent finding and occurred even when the transducer was angled so as to enter the left atrium a technique which would result in the tumor's crossing the beam early in its course As the balloon was increased in size it entered the left ventricle progressively earlier in diastole (Fig 2) however a delay between mitral valve opening and tumor prolapse still occurred despite very large tumor size (Fig 4)

Tumor mitral valve and septal contact The technique of coupled pacing to slow the heart rate was used in order to prolong diastole for better evaluation of mitral valve and tumor interaction Fig 5 illustrates how the tumor strikes the interventricular septum during diastole The first beat, with the balloon inflated, shows the tumor in contact with the septum The mitral leaflet enveloping the simulated tumor displays a hump at the end of diastole When the balloon is partially deflated the succeeding beat shows the anterior mitral valve leaflet receding from the septum and the disappearance of the hump Its absence in the second beat suggests the possibility that the hump represents a prominent A wave and confirms its dependence on the presence of the tumor This hump can also be seen in all three beats of Fig 4

Discussion

The commonly accepted statement[10] that the E to F slope is decreased at least to a mild to moderate degree in atrial tumor seems to be dependent more upon the size of the tumor than its presence The mechanism for the decreased E to F slope is due to the fact that the prolapsing tumor maintains the mitral valve in the open position during the entire diastolic phase Thus one would expect the size of the tumor to play a significant role in determining the E to F slope As one would predict large tumors resulted in marked reduction or reversal in the E to F slope (Fig 2) However as clearly shown (Fig 1) a rapid E to F slope is compatible with the presence of a tumor

It is important to note that based on this model a normal E to F slope should not be construed as ruling out a left atrial tumor by erroneously labeling the echoes behind the mitral valve as artifacts Fig 3 demonstrates how this problem can be resolved One should obtain the echocardiograms by angling the transducer to

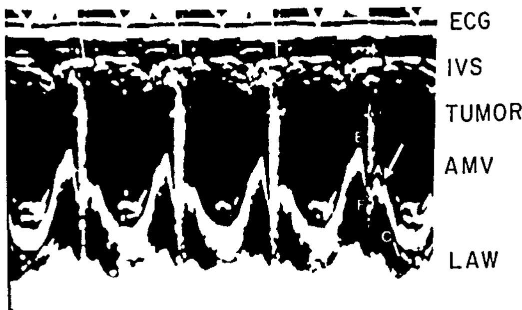


Fig 1 This illustrates a normal E to F slope in the presence of a small atrial tumor Arrow points to the notch on the AC component ECG = electrocardiogram IVS = interventricular septum AMV = anterior mitral valve leaflet and LAW = left atrial wall Abbreviations are the same in all figures

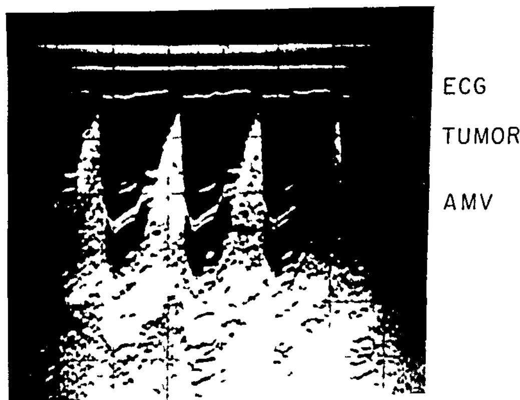


Fig 2 The E to F slope is reversed in the presence of a large atrial tumor

mobility of the tumor can be visualized The transducer is angled in order to pass through the anterior mitral leaflet and the left atrium Usage of this technique allows the tumor to be seen in both systole and diastole as it moves from the left atrium to the left ventricle behind the mitral leaflet

The AC notch or plateau A notch on the AC component of the anterior mitral leaflet echo was found (Fig 1) Note the absence of this notch or plateau in Figs 4 and 5 where the tumor is much larger In fact the AC component appears to have a much more rapid downward slope as the tumor size increases The exact moment indicating the onset of mechanical systole is marked by the abrupt posterior motion of the interventricular septum in Figs 4 and 5

The early diastolic echo free interval There

should also be expected The abnormal notched downstroke following atrial systole with small simulated mobile left atrial tumors has several possible mechanisms (1) Prolongation of the PR interval may permit a transient pause in the normal uninterrupted posterior movement of the anterior leaflet following atrial systole before ventricular contraction completes mitral valve closure (2) Left atrial decompression following diastolic prolapse of the tumor into the ventricle results in a shortened A wave following which mitral leaflet posterior motion ceases until ventricular contraction begins (3) The normal pressure relationships between the left atrium and left ventricle toward the end of diastole may be altered by the additional diastolic volume increment due to the presence of the tumor This reversal in the normal diastolic gradient may be sufficient to cause presystolic expulsion of a small tumor from the ventricle and result in a notched AC slope Large tumors which do not display the *AC notch* require left ventricular contraction for expulsion (4) Konecke and co workers[12] in a study performed in humans in which simultaneous echocardiograms and left ventricular pressures were recorded, found that if the left ventricular initial diastolic pressure (LVIDP) was normal and the left ventricular *end diastolic* pressure (LVEDP) was elevated a plateau was recorded on the AC component of the anterior mitral valve leaflet echocardiogram They postulated that this was related to the sudden increase in ventricular pressure following atrial contraction leading to the early onset of mitral valve closure preceding ventricular systole Closure of the mitral leaflet would then temporarily cease at the point of equal pressures resulting in the plateau or notch until ventricular systole begins and closure is completed.

It would be of interest to watch for this notch in future cases of left atrial myxoma to define its origin The notch might aid in defining an abnormality where the zone of echoes suggesting a left atrial tumor is small and the E to F *slope is* normal a condition suggesting a false positive It is important to note however that this echocardiographic notch is not specific for any condition[12]

Pitt and co workers[13] in their analysis of left atrial pressure tracings in the presence of left atrial tumors suggested that the tumor entered the left ventricle at the moment the mitral valve opened followed later by blood The echocardiographic findings obtained in this study differ with their interpretation The delay in tumor prolapse was most marked in the case of small tumors (Fig 1) A possible artifact may result from the fact that the tumor must cross the sound beam before it is detected Fig 1 is taken with the transducer angled to enter the left atrium a position which would detect the tumor as soon as it crossed into the left ventricle The delay was still present With greater balloon inflation although the delay is less the early diastolic echo free interval is still present This suggests that the initial rapid y descent of the left atrial pressure curve is secondary to the entrance of blood into the left ventricle through a nonobstructed mitral orifice partially decompressing the left atrium The tumor then prolapses at a variable time depending on its size The increase in left atrial pressure at end diastole would thus still be secondary to obstruction of the mitral orifice by tumor although occurring later than suggested by Pitt and co workers[13]

Various authors have commented on mitral valve lesions in the presence of atrial tumors[14,15] These may be related to the gross distortion of the anterior mitral valve leaflet by the tumor as manifested by the end diastolic hump in Figs 4 and 5 a finding which has been described previously[5] The constant contact between mitral leaflet tumor and ventricular septum may explain the dislodgement of tumor emboli which is such an important part of the clinical picture of atrial myxoma[3]

Several clinical implications of this study are suggested Although the commonly accepted criteria for echocardiographic diagnosis were confirmed, two important variables which might cause confusion in cases of small tumors were found. The absence of a decrease in the E to F slope might lead one to overlook the thin column of accompanying echoes which can easily be called an artifact In addition the finding of a plateau on the AC component might be used as further evidence that the patient has intrinsic myocardial disease and again the thin column of echoes erroneously ignored Both these findings occur with small tumors which would be readily amenable to surgery[16]

Summary

An experimental technique for simulating left atrial tumors and their echocardiographic features is described. The echocardiographic demon

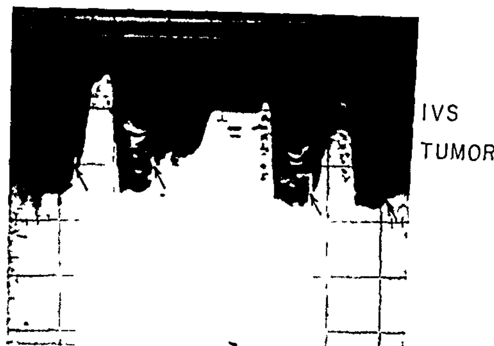


Fig 4 Large tumor results in a rapid smooth AC component A hump is present in all three beats The arrow points to the anterior mitral valve leaflet Coupled pacing is utilized to slow the heart rate

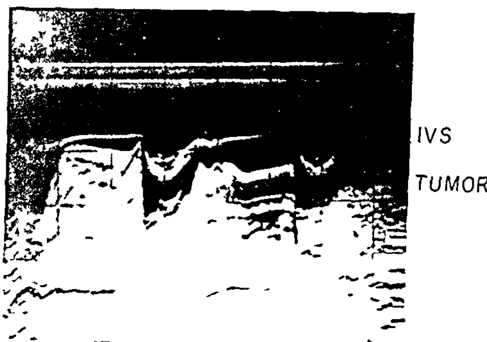


Fig 5 Arrow points to the hump on the anterior mitral valve leaflet which disappears following deflation (beat two)

pass through the anterior mitral leaflet and the left atrium This facilitates detection of a mass represented by a dense cloud of echoes which changes its position by prolapsing from atrium to ventricle Unfortunately this will not differentiate between a sessile left atrial tumor and a thrombus

A plateau or notch on the AC component of the mitral valve was seen during small degrees of balloon inflation and disappeared with greater degrees of inflation The explanation for the notch which interrupts the smooth posterior movement of the mitral valve leaflet following the termination of atrial systole is unclear The preservation of the normal E to F slope with small tumors indicates that the mitral leaflets are still responsive to the dynamic flow patterns which operate normally to cause rapid posterior displacement following early diastolic filling Therefore a normal response to atrial systole

The effectiveness of magnesium chloride in the treatment of ventricular tachyarrhythmias due to digitalis intoxication

Mohammad Farooq Ghani M D
John R Smith M D
St. Louis Mo

One problem of digitalis therapy is the common occurrence of intoxication One fifth of the patients receiving digitalis glycosides have been estimated to suffer intoxication at some time while taking it[1-5] To date a number of drugs have been used to control ventricular arrhythmias induced by digitalis however with unpredictable results and frequent undesirable side effects Of the newer anti arrhythmic drugs such as diphenylhydantoin lidocaine bretylium, and propranolol myocardial depression fatal arrhythmias or cardiac standstill have been reported refractoriness is an additional problem[1-6] In the event of life threatening ventricular arrhythmias induced by digitalis cardioversion or rapid ventricular artificial pacing have been considered, but these maneuvers are known to have their own hazards[1-5] Potassium is effective when ventricular irritability is associated with hypokalemia Similarly it is known that hypomagnesemia enhances digitalis toxicity[7] The present investigation however is addressed to the study of the effectiveness of magnesium chloride in persistent ventricular tachycardia induced by digitalis glycosides in the presence of normal serum magnesium levels

Materials and methods

Thirty nine healthy adult dogs of either sex weighing 17 ± 4.5 kilograms were divided into four groups to carry out the studies Thirty four animals were anesthetized with sodium pentobarbital 25 to 30 mg/per kilogram given intravenously Continuous Lead II electrocardiogram and arterial blood pressure were recorded on a multichannel Sanborn Recorder Catheters were advanced into the aorta and the pulmonary artery and the cardiac outputs were determined by dye dilution technique using indocyanine green (Cardiogreen) A persistent ventricular tachycardia was induced in Groups I and II by a standard dose of deslanoside (0 18 mg per kilogram) given intravenously Within 30 to 40 minutes the toxic rhythm was well established. Occasional brief episodes of ventricular flutter were also noted A group of five conscious dogs was used in another experiment as described later A 20 per cent solution of magnesium chloride in distilled water was prepared for parenteral use The cardiac output was determined in each animal before the digitalis solution was injected

Group I treatment of ventricular tachycardia with magnesium chloride In 19 dogs a persistent ventricular tachycardia lasting more than five minutes was induced by the standard bolus dose of deslanoside At this point a cardiac output was again measured for comparison with the control values Treatment with magnesium chloride (20 per cent solution) began with a 3 to 5 ml and followed with a 1 or 2 ml bolus intravenous injection given at 5 minute intervals until desirable results were obtained. After abolition of ventricular tachycardia and re establishment of a sinus rhythm the measurement of cardiac output was repeated. Ten milliliters of magnesium chloride solution was then injected intramuscularly and the intravenous administration was

F om the Departments of Medici nd Physiology and B ophysics, Washi gton U versity School of Medicine and U t I Medical Servic of the St. Louis City Hosp tal, St. Louis.

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Reprint requests Dr M. F Gha i, Associate Directo Ca di ascular Division, St. Louis C ty Hosp tal, 1515 Lafayette St. St. Louis, Mo 63104

stration of tumor movement between atrium and ventricle was noted in all cases and reliably detected the tumor A normal E to F slope could be seen in the presence of a tumor A notch or plateau was at times found on the AC component of the mitral valve echo and its hemodynamic implications are discussed The controversy concerning whether blood or tumor enters the left ventricle first during diastole is resolved in favor of the former The demonstration of tumor, mitral leaflet and ventricular septal contact provides a possible explanation for the presence of mitral valve lesions and tumor emboli in left atrial myxoma

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ride (Fig 1) When larger amounts of magnesium chloride such as 2 ml per minute by constant intravenous infusion were given in a group of five dogs the ventricular tachycardia was abolished however marked bradycardia ensued. Continued infusion over half an hour resulted in asystole in two dogs Intramuscular administration of magnesium chloride seemed to help maintain the regular sinus rhythm Once the sinus rhythm was well established ventricular tachycardia did not recur The electrocardiograms recorded on the second day invariably showed sinus rhythm and ventricular premature beats were rare

Control studies When the treatment with magnesium chloride was omitted the ventricular tachycardia always persisted on the same day and deteriorated into ventricular fibrillation in four dogs Treatment with lidocaine and diphenylhydantoin converted the ventricular tachycardia into a predominantly junctional rhythm in two of the five animals

Electrophysiologic effects of magnesium pretreatment Administration of magnesium chloride alone resulted in minor and transitory T wave changes in the electrocardiogram in two of five dogs No other electrocardiographic changes were noted with the dosage of magnesium used. The pretreatment with magnesium chloride prevented any arrhythmia and a regular sinus rhythm was maintained 30 minutes following a dose of deslanoside (0 18 mg per kilogram) which had invariably produced persistent ventricular arrhythmias in Groups I and II Deslanoside dosage larger by 83 3 per cent (total 0 33 ± 0 01 mg per kilogram) was then required to produce cardiotoxicity However ventricular tachycardia developed in only one of five dogs whereas serious A V conduction impairment and bradycardia developed in others leading to asystole Ventricular fibrillation did not occur

Hemodynamic studies The control cardiac output averaged 2 09 ± 0 22 L per minute (Fig 2) Five minutes after induction of a persistent ventricular tachycardia the cardiac output was reduced to 1 78 ± 0 21 L per minute (P < 0 05) In Group I after conversion of ventricular tachycardia into a sinus rhythm by treatment with magnesium chloride the cardiac output increased to 2 30 ± 0 39 L per minute (P < 0 01) In the pretreatment group a small (13 3 per cent) increase in the cardiac output 15 minutes after administration of magnesium chloride was found

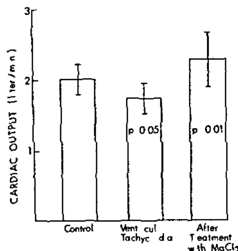


Fig 2 Cardiac output values (mean ± S E M) in the control state five or more minutes after induction of ventricular tachycardia by digitalis and after restoration of regular sinus rhythm by treatment with magnesium chloride

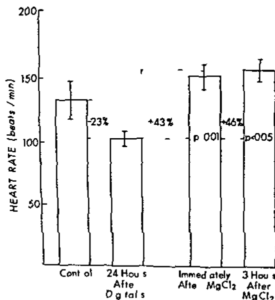


Fig 3 Changes in heart rate (mean ± S E M) 24 hours after administration of digitalis and then in response to magnesium chloride treatment

before digitalis administration The arterial blood pressure showed a slight but transient decline after intravenous injection of magnesium chloride

Biochemical studies The control serum magnesium level was 2 5 ± 0 1 mg per 100 ml There was no change in this value after ventricular tachycardia was established At the time of restoration of normal sinus rhythm following treatment the serum magnesium level was elevated

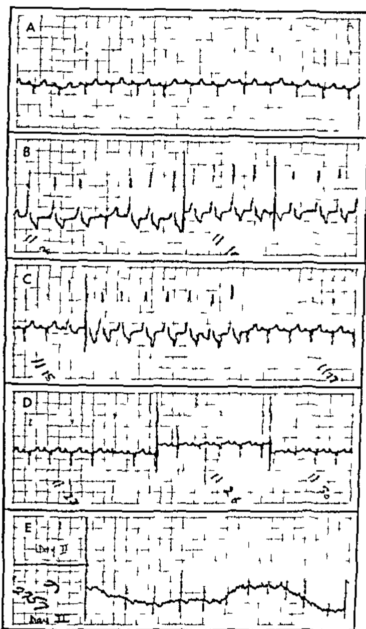


Fig 1 Reversal of digitalis induced ventricular tachycardia by magnesium chloride *A* a Lead II electrocardiogram in the control state *B*, persistent ventricular tachycardia half an hour after a standard toxic (see text) dose of deslanoside *C* sinus rhythm with ventricular premature contractions five minutes after initiation of $MgCl_2$ therapy *D* regular sinus rhythm re established 10 minutes after initiation of $MgCl_2$ therapy *E* sinus rhythm maintained on the second day

discontinued In five dogs a continuous intravenous infusion of magnesium chloride at a rate of 1 to 2 ml per minute was also used Serum magnesium levels were measured before administration of deslanoside, after induction of ventricular tachycardia, and again after the restoration of sinus rhythm in five dogs Similarly serum sodium potassium, chloride, and calcium values were also determined

Group II control experiments These studies in 10 dogs were conducted in the same way as described above, except that the treatment with magnesium chloride was omitted In five dogs after the ventricular tachycardia had persisted for 20 minutes lidocaine (200 mg intravenously) and diphenylhydantoin (250 mg intravenously) were administered.

Group III effect of magnesium pretreatment After control hemodynamic measurements pretreatment with a 10 ml intravenous and a 20 ml intramuscular injection of 20 per cent magnesium chloride solution was instituted in a group of five dogs The cardiac outputs were redetermined 15 minutes afterward and the standard toxic dose of deslanoside (0 18 mg per kilogram intravenously) was given After 30 minutes, additional doses of deslanoside, 0 05 mg per kilogram intravenous every 15 minutes were given until cardiotoxicity was observed

Group IV studies in conscious dogs The effect of magnesium chloride upon the serum glycoside levels and the electrocardiogram were studied in five awake dogs After recording the control electrocardiogram an intravenous bolus injection of 0 1 mg per kilogram of digoxin was given in order to determine the serum glycoside levels After 24 hours electrocardiograms were again recorded and treatment with magnesium chloride (10 ml intravenously and 10 ml intramuscularly of 20 per cent solution) was instituted. Venous blood samples for serum glycoside levels were obtained immediately before and one hour after administration of magnesium chloride The electrocardiographic monitoring was continued for three hours after the treatment At the end of the experiment, hemoglobin and hematocrit values were also measured for comparison with the control animals which were determined before administration of digoxin

The data obtained from these experiments were analyzed by paired t test to assess the statistical significance of the results

Results

Effect of magnesium chloride on digitalis induced ventricular tachycardia In 19 dogs treatment with 6 6 ± 1 4 ml of magnesium chloride (20 per cent solution) eliminated the ventricular tachycardia and a supraventricular rhythm occurred in 9 9 ± 1 8 minutes after initiation of the therapy After 20 7 ± 4 1 minutes a normal sinus rhythm was restored with a total dose of 11 7 ± 1 9 ml of intravenous magnesium chlo

mature beats prevailed Usually the ectopic ventricular beats decreased in frequency as the sinus rate increased. It appears therefore that the sinus pacemaker tissue may take some time to re establish dominance A moderately rapid injection of magnesium salt was observed by Boyd and Scherf[10] to be more effective than a slower injection and they postulated that a certain level of magnesium concentration that reaches the myocardial circulation may be important for its antiarrhythmic action

Solutions of magnesium sulfate in concentrations of 10 to 20 per cent used in dosages up to 20 ml intravenously have been found to be safe in normal human subjects as well as in cardiac patients[9 10 14] Much larger doses associated with markedly increased serum magnesium levels may cause untoward effects Tachycardia occurs at 2 to 5 mEq per liter prolongation of the PR interval at 5 to 10 mEq per liter widening of the QRS complex at 5 to 10 mEq per liter occasional SA and A V block above 15 mEq per liter respiratory failure at 17 to 28 mEq per liter and cardiac arrest at 27 to 44 mEq per liter[15] Such magnesium levels in the serum or the side effects did not occur with a dosage of magnesium chloride employed in our experiments On the other hand cardiac output increased by 13 3 per cent following magnesium pretreatment probably due to lowering of peripheral vascular resistance[16]

Possible mechanisms of action The action of magnesium ion upon the heart appears to be complex We did not find any significant change in the serum calcium sodium potassium chloride or digoxin levels following treatment with magnesium chloride Pretreatment with magnesium clearly rendered the heart resistant to digitalis toxicity The possible mechanisms of action may involve changes in the membrane permeability to various ions Magnesium may also enhance the activity of membrane associated sodium potassium ATPase of which it is a metallocoenzyme or reverse a digitalis induced inhibition to allow an inward flux of potassium[13] The same effect may also be achieved by a direct depression of potassium efflux by magnesium without the involvement of the sodium potassium exchange cycle[17] Since the prevention of efflux of potassium by the glycoside is not necessarily associated with the occurrence of arrhythmias other mechanisms may be operative[13] Magnesium is a most abundant intracellular cation second only to potassium and may due to its antagonism to calcium, decrease the intracellular content of calcium to abate the digitalis toxicity[18 19] There is also substantial evidence that magnesium can cause autonomic blockade[20 21] This blockade may be responsible for an increase in the heart rate due to abolition of vagal overactivity from digitalis Also by inhibition of sympathetic ganglia and perhaps by modification of the adrenergic system at the local level in the heart it may decrease cardiac irritability which will be further suppressed by an increase in the heart rate A direct suppressant action upon the ventricular automatic tissue is yet another possibility

It is therefore suggested that magnesium chloride may be a valuable form of therapy in digitalis induced ventricular arrhythmias as well as in prevention particularly in patients with cardiac disease who are apt to be deficient in magnesium

Summary

Efficacy of magnesium chloride in treatment and prevention of digitalis toxicity was studied in 39 dogs A persistent ventricular tachycardia lasting more than five minutes was induced in 29 dogs by deslanoside 0 18 mg per kilogram intravenously In 19 animals administration of magnesium chloride (5 to 10 ml of a 20 per cent solution) administered intravenously converted the ventricular tachycardia into a sinus rhythm. The cardiac output was found to be increased following this treatment (P < 0 01) The serum electrolytes and digoxin levels remained unchanged With larger doses of magnesium chloride significant bradycardia occurred in two instances following abolition of ventricular tachycardia When pretreatment with magnesium chloride (10 ml intravenously and 20 ml intramuscularly of a 20 per cent solution) was employed in a group of five dogs prior to administration of deslanoside ventricular tachycardia from the usual or greater doses of the glycoside was invariably prevented Deslanoside dosage larger by 83 3 per cent was then required to produce cardiotoxicity however VT appeared in only one out of five dogs whereas serious A V conduction impairment was seen in other dogs. None of the magnesium pretreated animals developed ventricular fibrillation in spite of marked bradycardia. In 10 dogs used as control animals,

Table I Laboratory values (mean ± S E M) in the control state and after treatment with magnesium chloride

	*Magnesium** *(mg/100 mL)*	*Calcium* *(mg/100 mL)*	*Potassium* *(mEq/L)*	*Sodium* *(mEq/L)*	*Chloride* *(mEq/L)*	*Digoxin* *(ng/mL)*	*Hemoglobin/hematocrit*
Control	2 5 ± 0 13	10 5 ± 0 09	3 9 ± 0 13	144 ± 0 5	117 ± 2 9	4 37 ± 0 89	13 4/42 4
After treatment with $MgCl_2$	3 1 ± 0 18	10 5 ± 0 12	4 1 ± 0 17	140 ± 1 3	121 ± 1 8	3 47 ± 0 47	13 0/4? 0

Only the magnesium values were significantly changed (P < 0 025) On the second day the magnesium level was 3 1 ± 0 10 mg per 100 ml and 2.8 ± 0 12 mg per 100 ml on the third day

to 3 1 ± 0 2 mg per 100 ml (P < 0 025) On the third day, the magnesium level returned toward control values while a sinus rhythm was maintained (Table I) The serum sodium potassium chloride and calcium levels remained unchanged by magnesium treatment (Table I)

Studies in the conscious dogs In Group IV a 23 per cent decrease in the heart rate was seen 24 hours after digoxin administration (Fig 3) The electrocardiographic evidence of digitalis excess or toxicity was present in all animals A Wenckebach phenomenon was noted in four dogs as evidenced by group beating and junctional beats with a leftward deviation of the QRS axis was present in one dog Immediately following the treatment with magnesium chloride a regular sinus rhythm was established and there was a 43 per cent increase in the heart rate which was maintained at even higher rates three hours later (P < 0 005) The serum glycoside concentration 24 hours after intravenous digoxin was 4 37 ± 0 89 ng per milliliter and one hour following the treatment with magnesium chloride this value averaged 3 47 ± 0 47 ng per milliliter The differences in serum digoxin levels of these paired determinations are statistically insignificant

Discussion

Digitalis toxicity is known to be precipitated by hypomagnesemia in experimental animals [7] Similar observations have been made in man [7,8] Administration of magnesium under these circumstances effectively controls the digitalis induced arrhythmias however, in most instances the status of magnesium has not been investigated [8,10] This question becomes even more important as the clinical use of digitalis is usually concomitant with that of the diuretic agents which produce hypomagnesemia Furthermore the serum magnesium levels may be normal when its cellular content is low, conversely, hypomagnesemia can occur in the presence of normal total body magnesium stores [11] Therefore the success of magnesium salts in the correction of digitalis toxic arrhythmias may only have been due to the replenishment of this cation as in the replacement of potassium in the presence of hypokalemia In our study, magnesium depletion or other conditions, such as hypercalcemia hypokalemia, myocardial injury etc are not the likely influencing factors. In addition the endpoint of cardiotoxicity in the present study is a persistent ventricular tachycardia lasting more than five minutes as compared to ventricular irregularities, A V dissociation or nodal tachycardia designated by others which can be induced by considerably smaller doses of cardiac glycosides [7,12,13]

Dosage and therapeutic considerations The concentration of the magnesium chloride solution and the dosage appear to be important determinants of efficacy Boyd and Scherf[10] found a 20 per cent solution of magnesium sulfate to be more effective than a 10 per cent solution In dogs Stanbury and Farah[12] made a few observations without control studies and obtained variable results They concluded that magnesium may temporarily restore a normal sinus rhythm in digitalis toxicity In a recent report Neff and coworkers[13] observed the occurrence of arrhythmias in 60 per cent of the animals when acetyl strophanthidin and magnesium sulfate were administered simultaneously however magnesium treatment was not repeated. When we used a constant infusion with larger doses, the ventricular tachycardia was abolished and although bradycardia followed in a few animals ventricular ectopic beats were rarely noted. Effectiveness of magnesium chloride was enhanced when intermittent intravenous bolus doses were used With this method there was a period when sinus rhythm intermingled with ventricular pre

Case reports

A case of pre-excitation

David Scherf M D
Carl Bornemann M D
New York N Y

Mr E E F a 57 year old insurance adjuster had a past history of being in perfect health like a bull, save for malaria in Southwest Asia at age 29 a duodenal ulcer at 39 when he gave up cigarettes palpitations since 31 when his heart would pop like hell go fast for two or three minutes starting and stopping suddenly and an electrocardiogram at 55 showing pre excitation. He was hospitalized two hours after he awakened at 1 00 A M with an episode of shortness of breath tightness across the anterior chest nausea, and vomiting attributed to myocardial infarction

The hospital course of thirteen days which was afebrile save for a rise to 101 F 36 hours after admission was marked by a blood pressure elevation initially to 200/100 and 160/90 falling within a few hours to remain subsequently between 130/80 and 110/70 no pain after an injection of 75 mg of meperidine hydrochloride on admission no leukocytosis but a slight shift to the left on the differential count a blood sugar of 125 mg per cent and cholesterol of 200 mg per cent on admission elevation of the SGOT from 37 on admission to 107 on the second day and to 55 on the third day and increase in the CPK to 27 5 on admission day 53 on the second day and 25 5 on the third day

Serial electrocardiograms showed on admission pre excitation, Type A (Fig 1) with a P R interval of 0 12 second and QRS complexes with a width of 0 14 (measured in Lead II) the RS T segments and T waves were abnormal particularly in the chest leads On the next day the electrocardiogram was changed (Fig 2) The delta waves were the same but the large R wave in Lead V_1 disappeared. The P R intervals remained 0 12 second and the QRS complexes had a width of 0 11 second (measured in Lead II) The RS T segments and T waves were normal on the third day (Fig 3) when the P R interval was 0 20 second Most of the beats failed to show the pre excitation pattern, except for occasional beats in the chest leads QS waves were registered in Leads III and aV_F with minimal elevation of the RS T segments in the same two leads On the eighth day the tracing showed isoelectric RS T segments but was otherwise unchanged from that on the third day Treatment included a continuous drip of 2 000 mg daily of lidocaine in dextrose and water on 3 consecutive days

From the Departme t of M d cine New York Med cal Colleg N w Yo k C ty N Y nd Sharon Hosp tal, Sharon Conn

Rece ed f public tion June 20 1973

R pri t req ests to D vid Sch rf M D 55 East 86th St. N w Y k N Y 10028

Fig 4 shows the response in the three standard and 3 unipolar limb leads to right carotid sinus pressure during regular sinus rhythm which persisted throughout the observation period six weeks after the infarction. At the beginning Lead I shows 3 sinus beats with normal QRS complexes a width of 0 08 second and a P R interval of 0 16 second This increases to 0 20 second as the carotid sinus pressure slows the sinus rate The horizontal black line approximately indicates the duration of the carotid sinus pressure without the beginning and the end of the pressure coinciding exactly with the beginning and the end of the line Carotid sinus pressure slows the sinus rhythm and induces beats with a P R interval of 0 12 second and a width of the QRS complexes of 0 20 second. After a transitional beat ventricular complexes are seen with the same P R interval and the same delta wave but with a different form of the QRS complexes which exhibit a width of 0 12 second. In Lead II the first two ventricular complexes still show a P R interval of 0 12 second and an abnormal QRS complex with a delta wave Four normal ventricular complexes follow with the P R interval prolonged to 0 20 second during carotid sinus pressure These are succeeded by four complexes having a P R interval of 0 12 and a width of 0 20 second At the end of the carotid sinus pressure the same QRS T complexes appear as at the beginning of the strip and have the same delta wave as the preceding abnormal complexes Lead III discloses 5 sinus beats with a width of 0 08 second and an artifact distorting the fourth complex During carotid sinus pressure the QRS complexes again widens to 0 20 second and the P waves almost disappear A transitional complex occurs at the end of the carotid sinus pressure followed by small QRS complexes with an identical delta wave The unipolar limb leads undergo similar changes during and after carotid sinus pressure as did the standard leads In each lead carotid sinus pressure elicits two forms of ventricular complexes One very wide with maximum carotid sinus pressure the other with the same P R interval and the same delta wave at the end of pressure but less wide and with a different configuration

Fig 5 presents the chest leads (V_1 to V_4 and V_6) A normal QRS complex is found at the end of Lead V_1 During carotid sinus pressure abnormal ventricular complexes manifest a width of 0 20 second. The transitional complexes seen at the beginning and end of the wide QRS deflections share the same delta waves and P R intervals with these deflections In Lead V_2 two normal ventricular complexes precede beats of a different morphology with short P R intervals and wide complexes at the height of carotid sinus stimulation. All the abnormal complexes have the same delta wave In Lead V_3

the ventricular tachycardia either persisted or deteriorated into ventricular fibrillation. In conclusion, the experimental data demonstrate that magnesium chloride is effective in treatment of digitalis induced ventricular arrhythmias

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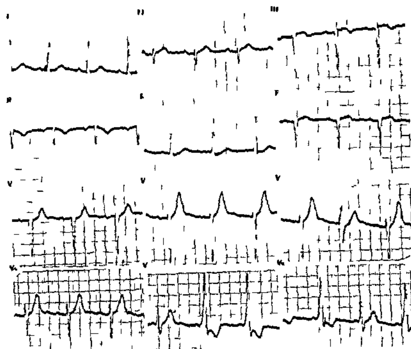


Fig 3 The electrocardiogram taken on the third day of hospitalization shows single pre excitation beats only in Leads V_3 V_5 and V_6 In the Leads III and aV_F deep Q waves with elevation of the RS T segments are seen

Whenever pre excitation beats appeared spontaneously the QRS complexes exhibited only a width of 0 12 second as illustrated immediately at the start and after the completion of the pressure The form of the wide QRS complexes noted only during carotid sinus pressure differed from those observed on the first and second days of hospitalization (Figs 1 and 2)

Discussion

Almost general agreement holds that abnormal QRS complexes preceded by a short P R interval result from impulses bypassing the A V node over an abnormal A V connection [1,2] The question arises which connection best explains the features of our case

Figs 1 and 2 show pre excitation Type A Figs 4 and 5 an example of pre excitation Type A with positive delta waves in all chest leads occurring not spontaneously but invariably induced by carotid sinus pressure The appearance of the pre excitation during carotid sinus pressure is a common phenomenon explained by a stronger vagus (acetylcholine) effect on the A V conduction system than on the abnormal by pass connection[3,4] however Laham[5] considers the occurrence of pre excitation during carotid sinus pressure to be the exception

Very wide QRS complexes registered only when the cardiac rhythm slows have occasionally been observed[6-10] Usually they have been described as a bundle branch block pattern emerging paradoxically after longer diastoles None of the various interpretations of these tracings have been entirely satisfactory An attractive explanation would be to invoke Phase 4 depolarization in the bundle branches which by reducing the membrane potential as the sinus impulse spreads over the heart alters excitability and conduction possibly causing block [11] If this explanation were valid the occurrence of bundle branch block after prolonged diastoles should be a common observation while in fact it is a great rarity Although this mechanism could be assumed to be present in Lead I of Fig 4 its application in Lead II falters During carotid sinus pressure in Lead II the diastoles lengthened from 103 to 121 After discontinuance of carotid sinus pressure in the second part of the tracing the QRS resumed its original configuration even after diastoles of 120 (in hundredths of a second) Likewise in Lead aV_R wide QRS complexes appear with diastoles of 97 or 96 during carotid sinus pressure but disappear with diastoles of 98 and 104 Consequently this phenomenon of wide QRS complexes is a function

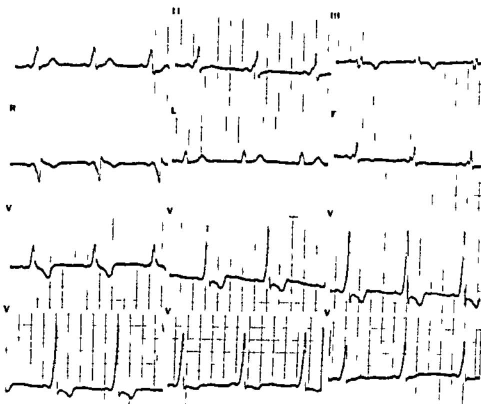


Fig 1 The 12 lead electrocardiogram obtained on admission shows pre excitation Type A

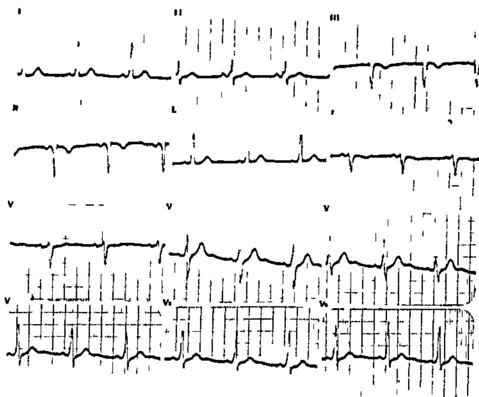


Fig 2 The 12 lead electrocardiogram taken on the next day shows the same delta waves and P R intervals and changes of the ventricular complexes

where only the first and last complexes are normal and in Lead V_4 the changes caused by carotid sinus pressure are like those in the other leads At the beginning of Lead V_6 two normal ventricular complexes display a progressive increase of the P R interval with blocking of the third P wave Abnormal QRS complexes follow with a gradual decrease of their width from 0 20 to 0 12 second the delta wave remaining unchanged Four ventricular complexes were deleted to show in the second part of the tracing the transition to a normal QRS complex with a normal P R interval

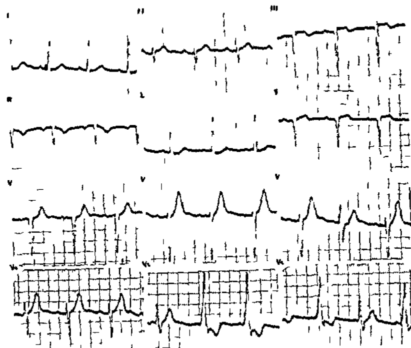


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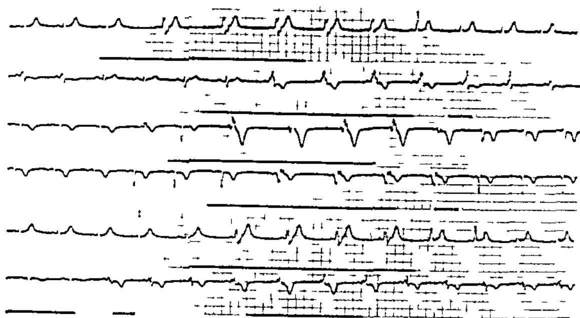


Fig 4 The three standard leads and 3 unipolar limb leads showing the effect of carotid sinus pressure The horizontal black lines indicate approximately the duration of the pressure See description in text

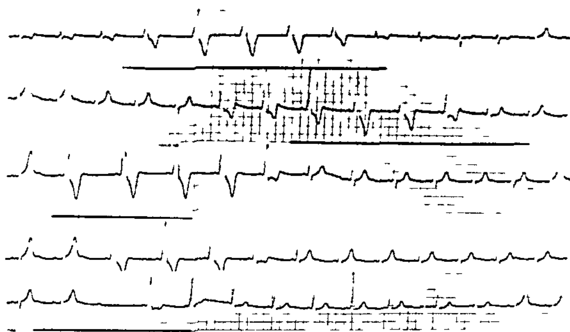


Fig 5 Leads V_1 to V_4 and V_6 again indicating the effect of carotid sinus pressure in Lead V_6 four ventricular complexes were omitted The horizontal black line in V_4 is covered by the tracing of V_6

of carotid sinus pressure and not of a prolonged diastole

According to one group of investigators Type A pre excitation indicates a bypass bundle between the left atrium and the left ventricular subendocardial layers [12] Boineau and Moore[13] asserted that right ventricular activation is premature Type A pre excitation because the accessory bundle first activates the right ventricle near its posterior aspects The delta wave is negative in III and aV_F, and positive in Leads I, II V_1 and V_6 [13] In our patient however the delta wave is positive in all leads with the exception of Lead aV_R

In Type B pre excitation the lateral border of the right ventricle has been found to be activated first,[14] whereas other studies led to the conclusion that the bypass in Type B is situated in the posterior part of the right ventricle [13] Confirming these findings in Type A pre excitation it was claimed that the left ventricle is activated first while in Type B the right ventricular activation

precedes [15, 16] We do agree that too few satisfactory studies are available to permit definite conclusions Sherf and James[17] postulated that the vagus by influencing one portion of the A V node more than the other induces abnormal activation of the ventricles because of a functional longitudinal dissociation of the conducting system The persistence of the form of the delta wave in our case before and during carotid sinus pressure speaks against this interpretation

Although in our tracing different P wave forms appear in some leads during carotid sinus pressure we do not believe that this fact relates to the appearance of pre excitation in our patient as it may in some other patients

Oehnell[18] described the widening of ventricular pre excitation complexes during carotid sinus pressure as a concertina effect. This encroachment of the delta wave on the preceding P R interval or its movement into or out of the QRS complex depends on the extent to which the impulse travels over the bypass or down the normal A V connection since the ventricles are often but not always excited partly via the normal A V system and partly over the bypass If the normal A V system is inhibited conduction over the abnormal bypass results in a wider ventricular complex with a more conspicuous delta wave Oehnell[18] differentiates three forms of the concertina effect. In the first the P S interval varies but the P waves remain constant. In the second, both the P S and P are constant while in the third, the form of the P waves varies

We reject Oehnell s[18] concertina effect as an explanation for our tracings because carotid sinus pressure in our patient widened the QRS and engendered two forms of ventricular complexes without changes in the P R interval or the delta wave During carotid sinus pressure the QRS widened from 0 12 second to 0 20 second with the P R intervals and delta waves remaining constant. Furthermore all leads especially the chest leads, clearly demonstrate that the two forms of ventricular complexes during carotid sinus pressure could not result from ventricular activation by the use of the normal pathway and a bypass bundle The transitional ventricular complexes at the beginning and at the end of the carotid sinus pressure should more or less approach the form of the pre excitation complexes before or after the pressure which is not the case No transitional complexes between the normally conducted beats and the pre excitation beats were observed

We cannot explain why the electrocardiogram observed on the first day of hospitalization (Fig 1) has not been duplicated on carotid sinus pressure during our studies Conceivably the pathophysiology of the acute myocardial infarction may have been responsible

The short P R interval and the delta wave indicate that A V conduction does not traverse the A V node but uses an abnormal pathway to excite the ventricles Since the delta wave retains its form and direction in both forms of abnormal QRS complexes appearing during carotid sinus pressure we must assume that the activation of the first part of the ventricles remains unchanged. To define which A V conduction would explain this phenomenon we may consider (1) a Kent bundle (a designation we apply to any abnormal bypass bundle connecting the atria and ventricle not connected with the normal A V conduction system) (2) a combination of James and Mahaim fibers and (3) a combination of James and Kent fibers

The effect of carotid sinus pressure described above in the presence of a Kent bundle only is unknown To utilize the concept of this connection in order to explain our case we would have to postulate a disturbance of intraventricular conduction during carotid sinus pressure

Carotid sinus pressure does as a rule not influence intraventricular conduction We know nothing about the innervation of the bypass (Kent) bundle but acetylcholinesterase has been found in the A V node and bundle of His [19,20] Several reports attribute certain electrocardiographic changes to a vagal or acetylcholine effect on the ventricle [8,9,21 23] which is denied by others During carotid sinus pressure investigators have repeatedly observed a paradoxical improvement" in A V or V A conduction For example return extrasystoles may occur only during carotid sinus pressure [24 6] Evidence supports the formation of ectopic impulses in the ventricle during carotid sinus pressure which can induce ventricular fibrillation [25 28] Experimentally faradic stimulation of the vagus in the neck can cause ectopic impulse formation in the ventricles which may result from release of catecholamines by acetylcholine [29 0] In one study in the dog no change of intraventricular pressure was found during intensive faradic stimulation of the vagi [31]

The vagal effect on the mammalian ventricle in complete A V block, in another study, was so slight that it "can be of but very little significance [32] On the other hand vagal stimulation slowed the ventricular automatic rhythm in the dog heart with complete A V block[33] and often slowed parasystolic ventricular rhythms[26] it caused a significant negative inotropic effect in other reports [34,35] Holzmann[36] observed widening of the delta wave during carotid sinus pressure which would indicate the possibility of an effect of carotid sinus pressure on intraventricular conduction

Hence the effect of carotid sinus pressure on intraventricular conduction is too ambiguous to serve as a satisfactory explanation for our observations, particularly because the form of the delta wave does not change during carotid sinus pressure

If an impulse were conducted through the James bypass fibers and then through the Mahaim bundles, the electrocardiographic pattern would be indistinguishable from one resulting from conduction through the Kent bundle [37] However, carotid sinus pressure, inhibiting conduction over the James fibers will change the delta wave while at the same time prolong the P R interval [38]

One could speculate that the conduction from the atria to the ventricles uses only a Kent bundle and the normal A V system all the time during carotid sinus pressure, because of inhibition of conduction over the normal A V conduction system a greater portion or most of the ventricles is activated over the Kent bundle If this were the case, the transitional ventricular complexes at the beginning and the end of the carotid sinus pressure should more or less approach the form of the pre excitation complexes before or after the pressure

We believe, therefore, that the most probable explanation for our patient's tracings is a combination of a Kent bundle and James fibers Conduction over the Kent bundle as well as over the James fibers causes a short P R interval The Kent bundle bypass causes early activation of a portion of the ventricular myocardium the delta wave During carotid sinus pressure and inhibition of conduction over the James fibers the Kent bundle alone activates the ventricles and causes the unusually wide QRS complexes With this combination the P R interval and the form of the delta wave would remain constant. We must assume that the first part of the ventricles is activated via the Kent bundle while the greater portion of both ventricles is activated a little later via the James fibers.

The pattern of spontaneous wide QRS complexes seen on admission (Fig 1) has not been observed again We cannot rule out transient intraventricular block caused by the acute myocardial infarction

Summary

A 57 year old man with paroxysmal tachycardias since 31 years of age and pre excitation discovered at age 55 was hospitalized at age 57 for a myocardial infarction Serial electrocardiograms showed Type A pre excitation as well as normal conduction The patient was studied six weeks after his infarction with carotid sinus pressure This induced Type A pre excitation having QRS complexes of two different configurations without a change in the P R interval or the delta wave best explained as resulting from inhibition of conduction over James fibers and activation over a Kent bundle only

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Coxsackie B_4 viruses and atrial myxoma

George E Burch M D
Lana L Shewey, M D
Joseph M Harb Ph D
New Orleans La.

Some viruses cause tumors in animals and man Myxosarcomas angiosarcomas and other connective tissue malignancies have all been transferred from animal to animal in cell free filtrates in order to satisfy Koch's postulates [1,2] However, to implicate viruses as etiologic agents in disease most virologists are satisfied either to isolate a virus from tissues blood or excreta of animals or man or to demonstrate a specific rise in antibody titer during the course of a disease [2] This report is concerned with the findings of numerous cells in an atrial myxoma which were stained deeply with Coxsackie B_4 virus immunofluorescent antibodies in addition to a viral type crystalline aggregate observed electron microscopically in the myxoma The significance of these findings is discussed below

Materials and methods

A section of the pedicle and base of a right atrial myxoma was collected immediately after it was surgically removed from a 54 year old woman The tumor weighed 49 5 grams and displaced 55 c.c of water It was dark red with large smooth lobulations (Fig 1) The myxoma was attached to the right atrium between the coronary sinus and ostium of the inferior vena cava Fresh tissue was obtained directly from the sterile operating table for light microscopy electron microscopy viral cultures and immunofluorescent staining for Coxsackie B_1 and B_4 viruses

From the Department of Medicine of the Tulane University School of Medicine and the Charity Hospital of Louisiana New Orleans La 70112

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Histology Portions of tissue from the pedicle and base of the myxoma were fixed in 10 per cent neutral formalin dehydrated and embedded in paraffin Sections 7 microns thick, were stained by routine hematoxylin and eosin method and examined by light microscopy

Electron microscopy Tissues prepared for electron microscopy included a portion of the body of the right atrial myxoma and a portion of the pedicle The tissues were minced into pieces approximately 1 mm ^{3} and placed in cold phosphate buffered 5 per cent glutaraldehyde for two hours followed by a three hour buffer rinse Postfixation was in cold 1 per cent osmium tetroxide in phosphate buffer for 1 5 hours Dehydration was accomplished with a series of methanol of increasing concentrations followed by three changes of absolute methanol at room temperature for 20 minutes each Embedment was in epoxy resin Thin sections were stained with aqueous uranyl acetate and lead citrate and examined with a Siemens Elmiskop I electron microscope

Viral culture Tissue from the myxoma was homogenized in a glass tissue grinder and inoculated into Wistar 38 roller tube cultures and porcine kidney (Y 15) cell lines from the Section of Infectious Diseases of the Department of Medicine Standard viral isolation techniques were employed.

Immunofluorescent staining A portion of the tissues was frozen and sectioned by cryostat Sections 12 microns thick were fixed in acetone for 10 minutes After being rinsed with phosphate buffered saline the sections were stained with fluorescein labeled rabbit antisera to Coxsackie B_1 and B_4 viruses for 45 minutes in a high humidity chamber in the dark They were again washed for 10 minutes in phosphate buffered saline before being examined with a Gillett



Fig. 1 Right atrial myxoma and pedicle (arrow) after surgical removal from a 54 year-old woman

Sibert fluorescent microscope which has a 12 volt Iodine Quartz lamp and a primary filter that allows no transmission below 370 mm in order to eliminate background fluorescence

Specificity of fluorescent staining was indicated by the fact that (1) tissue from the patient s left atrial appendage did not reveal cells that fluoresced and (2) the staining reaction was blocked when the sections were treated first with unlabeled antiserum and then with fluorescein labelled antiserum

Results

Histologic observations Light microscopic observations revealed myxoid stroma with much angiomatosis and blood pigment extending away from the pedicle There was very little small cell inflammatory reaction in the tumor There were however many large stellate cells and multinucleated giant cells that, from staining characteristics appeared to be mesenchymal in origin (Fig 2)

Electron microscopic observations. In the body of the tumor the predominant cell types were macrophages and myxoma cells The myxoma cells were widely scattered and single or in small cords of several closely apposed cells The tumor matrix contained abundant clumps of fibrous material and loosely arranged collagen fibers Macrophages many of which contained iron laden lysosomes were most numerous in the pedicle of the myxoma

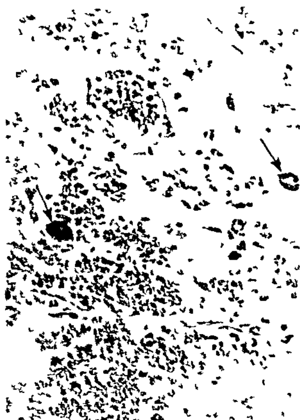


Fig 2 Light micrograph of a section from the base of the right atrial tumor showing large multinucleated tumor cells (arrows) and much angiomatosis (Hematoxylin and eosin, ×80)

Myxoma cells frequently contained cytoplasmic filaments sparse cisternae of endoplasmic reticulum and lysosomal bodies On occasion accumulations of particulate material were discernible within myxoma cell cytoplasm In such accumulations we observed a rosette type formation of particles which appear to be viral with 8 to 10 particles oriented around a dense particle core forming a crystalline configuration (Fig 3)

Viral cultures Attempts to isolate a virus were unsuccessful

Immunofluorescent observations Positive immunofluorescent antibody staining for Coxsackie B_4 virus antigen was observed abundantly in the cytoplasm of the large stellate cells of the tumor (Fig 4) This positive staining was blocked by unlabeled Coxsackie B_4 virus antibody Immunofluorescent staining for Coxsackie B_1 virus antigen was negative

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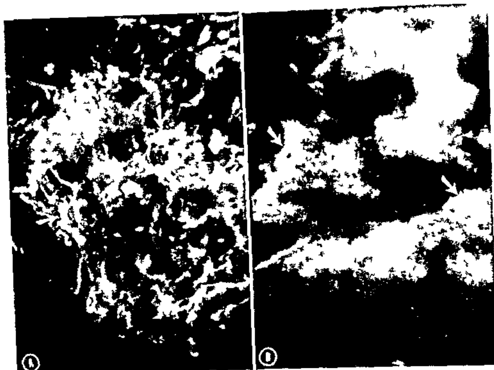


Fig 4 Immunofluorescent micrographs of a section from the base of the right atrial tumor showing dense fluorescent staining for Coxsackie virus B_4 in many large stellate cells (arrows) *A* ×80 *B* ×180

Discussion

The etiology of intracardiac myxomas is not known However the findings described in this report suggest a possible viral factor in the development and growth of such myxomas The immunofluorescent antibody staining observed in this study suggests very strongly that Coxsackie B_4 viral antigen was present in the stellate cells of the right atrial myxoma of the patient described. The finding of a rosette like arrangement of particles of Coxsackie viral size and orientation which closely resembles the rosette formation of Coxsackie B_4 viral particles observed in the pancreas of experimentally infected mice (Fig 5)[13] further indicates the presence of virus in the myxoma tissue It is possible that the viruses became attached to the myxoma after the myxoma had developed. Even though this concept must be entertained it is also equally possible that Coxsackie B_4 virus in this patient for yet unknown reasons was responsible for the development of the myxoma in the first place and that the virus continued to grow in this culture medium (the myxoma tissue) and was responsible for the continued growth of the tumor Surely these concepts cannot be settled on the basis of the findings in this one patient. As far as we know this is the first time anyone has even undertaken such an investigation for viral infection in an atrial myxoma There is a need to study the possible role of viruses in the production of this and other tumors of the heart of man

We are of the opinion that this and other similar tumors are virus induced First the appearance of this tumor both gross and histologic closely resembles that of the rapidly growing mucinous angiomatous and hemorrhagic tumors induced by the Rous sarcoma virus which initiated the concept in 1911 that neoplasia may be of viral etiology There was little or no inflammatory reaction in the tumor to suggest that the abundant intracytoplasmic viral antigen was a secondary invader of the tumor Furthermore there is a possibility that our antibody is not as specific as we think it to be Huebner and coworkers[9] and Armstrong Okuyan and Huebner[10] previously noted serologic similarities between viruses of the avian sarcoma leukosis group and influenza viruses However Payne Solomon and Purchase[11] found these viruses to



Fig 3 Electron micrograph of a portion of a myxoma cell from the pedicle region of the right atrial myxoma which was removed surgically Filamentous materials (F) and lysosomal bodies (L) help to identify this as a myxoma cell Accumulations of particulate material (C) are scattered throughout the cytoplasm In one such accumulation a rosette form (arrow) of apparent viral material is aggregated with several particles arranged circularly around a dense particle core (×24 000) This rosette like aggregate is further magnified (×66 000) and shown in the insert Compare with Fig 5

be very specific antigens when studied by immunofluorescent techniques The electron microscopic finding of the virus like particles with size and particle orientation similar to that previously noted by us in tissues of Coxsackie B_4 viral infected mice[12 13] supports the Coxsackie B_4 viral immunofluorescent observations.

Obviously much work needs to be done before all the questions concerning the possible role of viruses in the production of atrial myxomas can be answered. Nevertheless except for the fact that the single stranded RNA Coxsackie viruses seem to be independent of cellular DNA activity[14] we see no reason to discard our present findings which are strong though indirect evidence that the right atrial myxoma of our patient was caused by a virus There is a need to continue and to encourage similar and other studies of a possible viral etiology of atrial myxoma

An effort to culture the virus from the tumor failed Unfortunately the immunofluorescent and electron microscopic data had not yet been noted when the attempts to culture a virus were undertaken As a result only conventional procedures for viral isolation by culture were employed at the time Furthermore it is well known that viruses are often difficult to culture from autopsy material e g the hepatitis virus and other viruses.

Summary

Immunofluorescent antibody staining and electron microscopic studies revealed Coxsackie B_4 viral antigen and virus like particles in the cytoplasm of the stellate cells of a right atrial myxoma surgically removed from a 54 year old woman The hypothesis is presented that the virus was the etiologic agent and contributing factor in the continuing growth of the myxoma and that it was not present as a secondary infection of the tumor cells There is a need to extend these observations and continue such studies

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Fig 5 Electron micrograph of a portion of an interstitial cell from the pancreas of a newborn mouse killed one day after inoculation with 0 1 ml of Coxsackie B_4 virus culture fluid having a titer of 10 $^{8 5}$ $TCID_{50}$ Rosette like formations of apparent viral material are situated within a fibrous body of this cell (arrows) The rosettes are composed of as many as ten particles arranged circularly around a dense central particle This type of rosette pattern was frequently observed in the pancreas of infected newborn mice in association with cytonecrosis typical of infection with picornaviruses (× 68 400)

Seven patients also had congestive heart failure The murmur did not regress as the failure improved. Two patients in this group underwent surgery (Nos 21 and 43)

One patient (No 43) had early ankylosing spondylitis and another (No 40) had rheumatoid arthritis Both had systolic and diastolic murmurs. There was complete disappearance of the murmurs in Patient No 40 while Patient No 43 underwent open heart surgery and had an aortic valve replacement (see case history) All the patients included in the series represented, in the authors opinions examples of organic cardiac disorders which had developed for the first time after the onset of methysergide therapy and which had no other probable etiology

Clinical data

Of the 48 patients included in the series three have been selected to be presented in short case history form to give the reader a picture of the variety of medical histories presented by these patients Endocardial tissue became available for pathologic examination in four patients Detailed pertinent clinical data on the 48 patients are presented in Table I It has been difficult to grade and describe murmurs in this series in uniform fashion since information about patients other than those directly under the care of the authors was gathered from the records of many other physicians All the murmurs described in patients Nos 1 through 25 in Table I are graded on a scale of 1 through 6 as described by DeGowin and DeGowin [10] In the remaining patients the descriptions provided in other physician s accounts have been used and placed in quotation marks

The observation period extends from 1964 to 1970

Comment on Table I The minimum age of these patients was 30 years and the maximum 69 years Of 48 patients 31 had migraine headaches six had cluster headaches nine had combined headaches (migraine plus muscle contraction headaches) and two had muscle contraction headaches

The dose of methysergide used varied in most patients from 2 to 8 mg per day Sixteen patients received doses between 8 and 24 mg a day for short periods of time

The duration of methysergide administered before the murmur was first detected varied from seven months to 79 months The appearance of the cardiac murmur is not directly related to the dose or duration of drug administration (Patient No 43 received 6 mg a day for seven months only and Patient No 14 had taken only 2 to 3 mg per day of methysergide for 12 months when the murmur was detected)

The types of murmurs encountered are described in Table II

Patients were followed from six weeks to 74 months Most of the follow ups are between 20 and 40 months after stopping methysergide

Murmurs in each category offered examples of complete partial and no regression after stopping methysergide Table III records the progress of the murmurs after methysergide was discontinued.

Three patients underwent surgery One patient had no murmur but autopsy study was significant (see Figs 3 and 5 B) In two patients follow up is not available

Eleven patients had other fibrotic conditions possibly related to methysergide administration Two patients with murmurs also had pleuropulmonary fibrosis both of these patients being males Nine patients with murmurs also had retroperitoneal fibrosis (eight females and one male) There was partial or complete clinical laboratory and x ray regression in these related fibrotic conditions after methysergide was discontinued.

Laboratory data

Examination of routine laboratory data at the time when murmurs were first detected revealed no significant abnormalities with the following exceptions (1) one patient out of 17 had a hematocrit below 35 per cent (31 per cent) (2) six patients had corrected sedimentation rates above 25 mm out of 15 patients tested (3) five patients out of 15 patients tested had elevated BUN three of these five also had retroperitoneal fibrosis (4) C reactive protein was positive in one patient and negative in another patient (5) five patients were tested for antinuclear gamma globulins they were present in three and absent in two patients (6) lupus erythematosus preparation was done on seven patients all of them were negative (7) the latex fixation test was performed and found negative in two patients (8) cryoglobulins

Cardiac murmurs and endocardial fibrosis associated with methysergide* therapy

Dhirendra S Bana M D
Perry S MacNeal M D, F A C P
Philip M LeCompte, M D
Yogendra Shah, M D
John R Graham M D M A C P
Boston Mass and Philadelphia, Pa.

The occurrence of inflammatory fibrosis in the retroperitoneal space of patients taking methysergide for migraine was first reported in 1964[1] and has been confirmed in several subsequent publications[2-4] Examples of this uncommon disorder which have arisen during methysergide therapy in the past nine years have provided evidence which seems sufficient to link the two in a cause and effect relation

While this information has been accumulating examples have occurred of similar fibrotic processes taking place in the pleuropulmonary space and in the great vessels, heart valves and endocardium of some patients taking methysergide

This paper purports to present a summary of information available to us to date on patients who have exhibited cardiac abnormalities while taking this drug It includes data, and in some cases illustrations on several patients reported previously elsewhere[5-9]

The data consist of (1) observations of the development and progress of cardiac murmurs in 36 of our own patients taking methysergide (2) in 12 patients of other physicians who have kindly supplied us with information, (3) observations on cardiac murmurs occurring in nine patients with retroperitoneal and two patients with pleuropulmonary fibrosis occurring during methysergide therapy and (4) pathologic material obtained at surgery or autopsy in four patients.

Several patients have been excluded in whom information was not available as to the cardiac status of the patient before taking methysergide or in whom other conditions existed which seemed more likely to have been the cause of the development of cardiac murmurs In a few instances, patients were included who had other conditions which conceivably might have explained the development of murmurs These have been listed in Table I under the heading Possible other causes of murmur In such cases details of the history strongly suggested that this condition was not responsible for the murmur inasmuch as the evolution of the murmur had no relation to the course of the other condition The murmurs that were accompanied by congestive heart failure, hypertension or anemia, were included only if they did not disappear once these factors were corrected Ten patients had mild to moderate hypertension There was documentation of the absence of heart murmur in all of them prior to drug therapy In three of the hypertensive patients (Nos 13, 16 and 28) there was no change in heart murmurs after stopping the drug In one patient (No 19) the murmur grew worse in four patients there was partial regression of the heart murmurs after stopping methysergide

From the Department of Medicine and Pathology Faulkner Hospital Boston Mass and the Department of Medicine Pennsylvania Hospital Philadelphia Pa

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Reprint requests to Dr Dhirendra S Bana 1438 Centre St Roslindale Mass 02131

*Sansert (Deseril in Europe) manufactured by Sandoz Wander Pharmaceuticals Hanover N J

Murmurs	*Changes in murmurs after methysergide stopped*
1/6 high pitched systolic murmur at aortic and pulmonic areas radiating to both shoulders	55 mos later murmurs completely regressed
4 6 blowing systolic murmur at mitral area radiating to axilla and all over precordium	
3 6 systolic murmur at mitral area and 1/6 diastolic murmur at mitral area	18 mos later patient continued methysergide systolic murmur louder and diastolic disappeared
1/6 systolic murmur at the aortic area	2 mos later no change
2 6 diastolic murmur at the aortic area systolic murmur at the pulmonic area	47 mos later 2/6 diastolic murmur at aortic and at LBS
2/6 systolic murmur at mitral area and LBS 1/6 diastolic murmur at mitral area	26 mos later 1/6 diastolic murmur at mitral area
2/6 systolic and 2/6 diastolic murmur at aortic area 3/6 diastolic murmur at mitral area and at LBS	57 mos later 2/6 systolic and 1/6 diastolic murmur at aortic area 1/6 systolic and 1/6 diastolic in mitral area and 2/6 along LBS
1/6 systolic at mitral and 2/6 diastolic murmur at LBS	61 mos later 2/6 diastolic murmur at LBS RPF partially cleared developed hypertension
2 6 ejection systolic murmur in the aortic area and 1/6 diastolic murmur along LBS	8 mos later no murmurs heard
2/6 systolic murmur at mitral area and 1/6 diastolic murmur at LBS	50 mos. later 1/6 systolic murmur at mitral area and 1/6 diastolic murmur at LBS
1/6 systolic murmur at pulmonic and aortic area	6 mos later no murmur
1/6 diastolic murmur at LBS	23 mos later no murmur 1 + bruit over carotid
2/6 diastolic murmur at mitral area and at LBS	36 mos later 2/6 diastolic murmur at LBS definite improvement in pulmonary function
2 6 systolic murmur at pulmonic area	27 mos later no change
1/6 systolic murmur at pulmonic area and 1/6 diastolic murmur at mitral area and LBS	25 mos later 1/6 systolic murmur at pulmonic area
No murmurs patient died in Nov 1967 due to cerebral hemorrhage	9 mos later patient died necropsy revealed mitral and tricuspid valvular disease characterized by marked thickening and adherence to chordae absence of classic stigmata of both rheumatic and bacterial endocarditis (see text)

pulmonary area radiating to both shoulders Methysergide stopped.

Sept 1968 Murmur slowly regressed to Grade 1/6 at the apex only No angina or dyspnea

Dec 1969 Murmur entirely gone Patient has no cardiac symptoms

Patient No 6 Aortic murmurs in systole and diastole not regressing significantly after five years off drug A 43 year old female with common migraine 1+ systolic murmur heard twice in the past but no murmur at the time drug was started

Dec 1959 Methysergide started Dose range 1 to 16 mg average dose 10 to 12 mg daily

Jan 1963 A Grade 2/6 blowing diastolic murmur heard in the aortic area and left border of the sternum

Mar 1964 A Grade 2/6 systolic and Grade 2/6 diastolic murmur in the aortic area A Grade 3/6 diastolic murmur along the left border of the sternum and in the mitral area

May 1965 Methysergide discontinued.

June 1967 No change in the heart murmurs

Feb 1970 No cardiac symptoms. A Grade 2/6 systolic and Grade 1/6 diastolic murmur at the aortic area and a Grade 2/6 diastolic murmur along LBS A Grade 1/6 systolic and Grade 1/6 diastolic murmur at the mitral area

Patient No 44 Aortic murmurs cardiac failure retroperitoneal fibrosis Leriche syndrome all with partial regression (Also had fibrocystic disease of the breast) A forty nine year old *female with* a common migraine headache

Table I

No	Age Sex	Headache diagnosis	Methysergide daily dose (mg.)	Duration of treatment (mos.)	Possible other causes of murmur	Possibly related conditions
1	51 F	Combined headache	4	15	Nil	Anginal syndrome
2	44 M	Cluster	2 8	17	Nil	Nil
3	55 F	Cluster	2 6	32	Nil	R P F Leriche syndrome
4	60 F	Migraine status	12 20	25	Mild hypertension 190/90 systolic murmur recorded 1942 and 1961	Congestive heart failure
5	47 M	Common migraine and tension	8	36	Nil	Nil
6	43 F	Common migraine	1 16	43	Nil	Fibroid uterus
7	38 F	Migraine status	8 14	54	Nil	R P F
8	47 F	Common migraine	4 10	77	Mild hypertension	Red face and cheeks with prominent venules
9	50 F	Migraine status	2 10	26	Mild essential hypertension	Nil
10	38 F	Migraine status	2 8	24	Nil	R P F and fibroadenoma of breast
11	50 F	Common migraine	2 3	29	Nil	Pedal edema and bruit over aorta and femorals
12	60 M	Cluster	2 8	72	Nil	Emphysema duodenal ulcer keloids
13	47 F	Common migraine	4 8	40	Benign essential hypertension 180/110	Bruit over carotids and abdominal aorta
14	52 F	Migraine status and tension	2 3	12	Nil	Duodenal ulcer
15	40 M	Vascular headache	8 20	49	Nil	Nil

Abbreviations used LBS or LSB 4th intercostal space at left border of the sternum RPF retroperitoneal fibrosis PPF pleuro pulmonary fibrosis Patients 1 through 25 graded on scale of 1 to 6 patients 25 through 48 reported as described in records

were absent in two patients in whom the test was made (9) chest x ray showed an enlarged heart in seven out of 18 patients examined (10) all patients with *retroperitoneal fibrosis* had an intravenous pyelogram consistent with that diagnosis (11) the two patients with pleuropulmonary fibrosis had chest x rays consistent with that diagnosis (12) electrocardiograms were not abnormal in any specific way (13) 5 hydroxy indole acetic acid excretion was tested in four patients and was found to be normal and (14) immunoglobulin studies were performed on ten patients usually a considerable amount of time after methysergide was discontinued and revealed no striking specific abnormalities

Short case histories

Patient No 1 Development over one year of very loud aortic and mitral *systolic murmurs, slowly regressing completely* over four years after stopping methysergide A 51 year-old female with combined headache systolic murmur once heard during pregnancy in 1944 but no murmur heard since then in many examinations

Oct 1963 Started on methysergide 4 mg daily

Oct 1964 Acquired anginal syndrome dyspnea and a *systolic murmur (Grade 4/6) at the apex, pul*monary and aortic area

Jan 1965 A Grade 4/6 systolic murmur at the aortic and

Murmurs	*Changes in murmurs after methysergide stopped*
1/6 systolic murmur at mitral area	13 mos later no change
4 6 blowing diastolic murmur at aortic area and LBS 1/6 systolic and 1/6 diastolic murmur at mitral area	28 mos later 2/6 diastolic murmur at the aortic pulmonic and at LBS no systolic murmurs
2 6 systolic murmur at mitral pulmonic areas and at LBS	30 mos later no murmur
1/6 systolic murmur at mitral area and 1/6 harsh systolic murmur at LBS	24 mos later 3/6 systolic murmur at aortic area and over right clavicle R P F partially regressed
2 6 systolic murmur at mitral area early diastolic murmur at aortic area	38 mos later no murmurs
3/6 high pitched systolic murmur at mitral area radiating to axilla 2/6 late diastolic murmur at mitral area 2/6 decreasing end diastolic murmur at LBS	5 mos later patient underwent surgery with replacement of mitral and aortic valves patient died within 48 hours after surgery (see text pathology)
1/6 diastolic and 1/6 systolic murmur at aortic area	64 mos later 2/6 diastolic murmur at LBS
2 5 diastolic murmur at aortic area and at LBS 1/6 systolic murmur at pulmonic area	65 mos later 2/6 diastolic murmur at LBS
1/6 systolic murmur at mitral area	Patient committed suicide no necropsy
4 6 systolic murmur at mitral area	58 mos later 3/6 systolic murmur at mitral area
3 + apical systolic radiating to the axilla	30 mos later murmur still present
4 + mitral systolic murmur transmitted axilla	28 mos later murmur disappeared
3 + apical systolic murmur	27 mos later murmur persists
Aortic insufficiency murmur	39 mos later murmur still persists
1 + apical systolic murmur transmitted to the axilla	30 mos later murmur disappeared
Mitral systolic murmur	2 mos later murmur disappeared
3 + mitral systolic murmur transmitted to the axilla	27 mos later murmur persists
2 + apical systolic murmur transmitted to axilla	27 mos later murmur persists
3 + mitral systolic murmur	Patient continued methysergide for 7 mos after murmur was first detected murmur became louder 48 mos later murmur still persists
Aortic insufficiency murmur was detected	16 mos later murmur still present
Aortic insufficiency murmur	7 mos later murmur disappeared
1 2 short systolic murmur in aortic area	23 mos later no murmur heard

received methysergide for six months when she developed myocardial infarction congestive heart failure and aortic regurgitation After her condition stabilized cardiac catheterization and coronary angiograms were carried out which showed occlusion of the ostium of the left coronary artery and confirmed the aortic regurgitation

In Nov 1964 open heart surgery revealed the following findings (1) fibrotic thickening of the aortic root (2) degeneration and thickening of the aortic cusps (3) no dilation of the aortic root and (4) left coronary ostium reduced to a pore size

Within the wall of the thickened aortic root beyond this the coronary artery appeared free of disease and comparatively normal. Biopsy of the aortic valves revealed moderate irregular thickening of the free edges Microscopically a uniform deposition of fibrous tissue was seen on top of a normal appearing semilunar valve (Fig 1 *D*) Biopsy of the aortic wall revealed intimal and medial fibroplasia with marked patchy destruction of medial elastic tissue

Patient No 21 A 49 year old female No past history of heart disease began taking methysergide in late 1960 for cluster headaches In April 1963 she developed congestive heart

Table I—continued

No	Age Sex	Headache diagnosis	Methysergide daily dose (mg)	Duration of treatment (mos.)	Possible other causes of murmur	Possibly related conditions
16	52 F	Migraine status	8 12	64	Mild hypertension	Nil
17	69 F	Common migraine	2 10	79	Moderate hypertension	Congestive heart failure
18	41 F	Common migraine	4 8	48	Nil	Mild joint pains in spine and knees
19	53 F	Common migraine	6 8	45	Moderate hypertension	R P F urethral stricture bruits over abdominal aorta
20	41 F	Common migraine	16 20	55	Nil	Bruit over aorta and femorals
21	49 F	Common migraine and cluster headache	2 8	51	Nil	Congestive heart failure
22	40 F	Common migraine and tension	2 16	53	Mild hypertension	Subacute thyroiditis
23	40 F	Common migraine and tension	6	33	?systolic in childhood later in adult life no murmur before receiving methysergide	Nil
24	56 F	Migraine status	6 24	61	Nil	Nil
25	58 F	Migraine status	6 8	48	Nil	Congestive heart failure
26	41 F	Common migraine and tension	8 20	35	Nil	Nil
27	46 F	Migraine	8 12	30	Mediterranean anemia	Nil
28	41 F	Migraine	6 16	13	Mild hypertension	Nil
29	42 F	Migraine	8 12	12	Nil	Nil
30	51 F	Migraine	6	21	Nil	Nil
31	55 F	Migraine	8	21	Nil	Bruit over the abdominal aorta
32	48 F	Migraine	6 8	34	Nil	Nil
33	45 M	Migraine and tension	6 8	27	Nil	Nil
34	45 F	Tension	8	33	Nil	Nil
35	38 F	Migraine	8 16	10	Nil	Nil
36	47 M	Migraine	8	12	Hypertension	Nil
37	52 F	Common migraine	2 4	30	Nil	R P F fibrocystic lesions of breast urethral stricture

Oct 1964 Methysergide 6 mg a day started

Sept 1965 Intermittent claudication

Nov 1965 Fibrocystic disease of the breast

Feb 1966 Congestive heart failure 3+ decrescendo diastolic murmur at the left border of the sternum (LBS) 3+ ejection systolic murmur at the aortic area radiating into the neck and abdomen Aortogram—diffuse narrowing of aortic bifurcation IVP—evidence of retroperitoneal fibrosis Methysergide discontinued

May 1966 IVP—improvement in retroperitoneal fibrosis

Feb 1967 Decrease in the intensity of the aortic insufficiency continued improvement in retroperitoneal fibrosis Dyspnea still present on exertion Two pillow orthopnea

Pathology

Pathologic material was acquired largely in retrospect from four separate sources We would like to report the pathologic findings in some detail and present all the material that we have gathered so far on this subject Some of the lesions described here have been reported elsewhere [5 9]

Case histories of patients in whom material was obtained for pathologic examination

Patient No 43 This patient was a 30 year old female The patient had a classic migraine headache and rheumatoid like arthritis She had

Murmurs	Changes in murmurs after methysergide stopped
2 + apical systolic murmur and mild congestive heart failure and evidence of myocardial ischemia cineangiogram showed absence of some branches of left coronary artery	74 mos later murmur persists cardiac function improved
Aortic stenosis	Unknown
2 3 + systolic and diastolic murmur best heard in third and fourth Lics 3 4 + systolic murmur heard loudest at the apex	43 mos later murmurs disappeared completely partial regression of R P F
3 + blowing apical pansystolic murmur radiating to LSB and left axilla	6 weeks later no change
A very loud systolic murmur at apex a to-fro murmur in the mitral area a systolic murmur heard at the base 2 + blowing diastolic murmur heard along LSB	7 days later systolic murmur disappeared 21 mos later 1 + diastolic murmur along LBS
3 + decrescendo diastolic murmur at the base and systolic ejection sound	5 mos later a Starr Edwards aortic prosthesis was inserted 26 mos later 3 + systolic and diastolic murmur in the aorta area along LSB 2 + systolic murmur at the apex click of the valve patient had an uneventful delivery of a healthy baby after surgery (see text pathology)
3 + decrescendo diastolic murmur along LBS 3 + precordial ejection systolic murmur in the aortic area radiating into the neck	6 weeks later R P F markedly improved 12 mos later gradual improvement in the intensity of the murmur of aortic insufficiency
3 + systolic murmur at the apex	11 mos after murmur first detected patient underwent open heart surgery with replacement of mitral valve with Starr valve prosthesis valve showed marked fibroplastic endocardial thickening of mitral valve and chordae tendineae 2 mos postoperative patient developed leak around valve and needed open heart surgery again (see text)
3 + blowing apical systolic murmur	10 mos later 2 + murmur persists satisfactory clinical regression of R.P F
3 + aortic diastolic murmur 2 + apical systolic murmur 1 + aortic systolic murmur	17 mos later aortic diastolic murmur still present no systolic murmur heard
1 + diastolic murmur heard in the fourth Lics	25 mos later no murmur heard, pulmonary functions improved

Methysergide was discontinued in Feb 1966 because of transient cerebral ischemic attacks. In Nov 1966 he died following a massive in tracerebral hemorrhage No heart murmurs were ever noticed and no other cardiac abnor mality was ever detected.

Postmortem examination revealed the mitral valve to be quite abnormal Its cusp while having a free delicate edge was irregularly thickened due to fibrosis and on its ventricular surface there were fused or adherent chordae One of the chordae measured 3 mm in diameter The en docardial surfaces of the valves showed no evi dence of rheumatic stigmata and there were no MacCallum s patches nor evidence of active or healed endocarditis bacterial or rheumatic

The valve leaflet is shown in gross in Fig 4 *B* Although the gross appearance is very similar to that of the rheumatic valve shown on its left (Fig 4 *A*) and the carcinoid valve on its right (Fig 4 *C*) the microscopic examination of this valve (Fig 3) reveals that its thickening is due to a sheet of dense collagen tissue (*d*) superimposed on an otherwise normal mitral valve (*c*) rather than to disruption of valve structure by inflam mation and fibrosis in the valve itself

Examination of the chordae as shown in Fig 3 reveals that the thickening is due to a uniform concentric ring of dense collagenous tissue (*a*) surrounding the core (*b*) which represents the original chordae tendinae It will be noted that the ring of collagen around this chorda is similar to that found in the other cases of methysergide induced fibrosis (Fig 4 *H*) rheumatic heart dis ease (Fig 4 *G*) and carcinoid heart disease (Fig 4 *I*) The tricuspid valve measured 11 8 cm in

Table I—continued

No	Age Sex	Headache diagnosis	Methysergide daily dose (mg)	Duration of treatment (mos)	Possible other causes of murmur	Possibly related conditions
38	42 F	Migraine and tension	2 6	14	Nil	Mild congestive heart failure and anginal syndrome
39	46 F	Migraine	?	?	Nil	? Breast lesion ? thyroid lesion
40	36 M	*Cluster*	16	18	Rheumatoid arthritis	R P F and bruits over the femorals
41	35 F	Tension	6	8	*Nil*	*Nil*
42	67 F	Common migraine	2 4	24	Nil	R P F
43	30 F	Classic migraine	6	7	Early ankylosing spondylitis	Coronary insufficiency myocardial infarction ventricular aneurysm
44	49 F	Migraine	6	16	Nil	Fibrocystic disease of breast congestive heart failure systolic bruit over femorals R P F ? right upper lobe infiltrate
45	40 F	Migraine	6	48	Nil	Nil
46	55 F	*Combined headaches*	6 8	20	Nil	R P F
47	50 F	Common migraine	2 4	44	Nil	Nil
48	47 M	Cluster	Dose unknown	16	Nil	P P F

failure and had murmurs of mitral stenosis aortic stenosis and regurgitation Methysergide and dihydroergotamine were stopped in Jan 1965 In March 1965, she underwent open heart surgery Unfortunately, the patient died the next day

Pathologic examination of the heart revealed it to be moderately dilated and weighing 550 grams The base of the aorta was thickened and the aortic valve was incompetent The mitral valve was greatly thickened and stenotic Fig 2, *D* shows a microscopic section of the aortic valve which, in itself, is intrinsically normal, but is altered by the superimposition of a thick plaque of dense orderly collagen tissue closely resembling the findings in the other methysergide induced cardiac lesions

There was evidence of old left ventricular wall myocardial infarction Coronary arteries showed rather advanced arteriosclerosis with much fibrosis hyalinization, and many granules of calcium pigment The lumen was markedly narrowed. The base of the aorta was not dilated. It showed very minimal atheroma but at some points the wall appeared to be thicker than usually seen Many parts of the aorta also showed evidence of cystic medial necrosis with increased prominence of the capillaries of the outer portions of the aorta surrounded by small groups of lymphocytes and plasma cells

Patient No 15 A 40 year old tool and die worker who was plagued with uncommonly severe migraine headaches Methysergide was started in Jan 1962 at 12 mg daily Two months later this was increased to 24 mg daily In addition he was taking ergotamine tartrate and caffeine tablets (Cafergot Sandoz Wander)

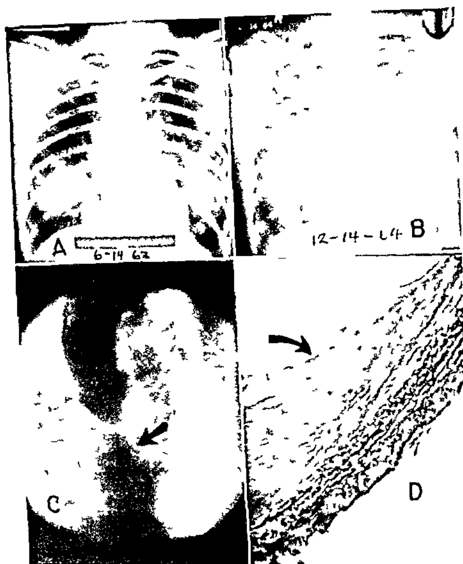


Fig 2 Patient No 21 *A* and *B* demonstrate the increase in the size of the heart from the time when the murmurs were first heard and symptoms developed until the patient was sent for catheter studies because of intractable congestive heart failure Both mitral and aortic valves were involved *C* shows the marked aortic regurgitation (arrow) and *D* illustrates the deposition of orderly collagen (arrow) on an otherwise normal aortic valve (X rays angiograms and pathologic specimen provided through the courtesy of Dr Clair E Basinger of the Blodgett Memorial Hospital Grand Rapids Mich Fig 2 *D* from J R Graham[7] Fig 10 p 32 courtesy of the American Journal of Medical Sciences)

chordae are fused to form bundles 4 and 5 mm in diameter No plaques or vegetations are present

Microscopically the valve edge between the chordae shows a marked fibroblastic thickening at the periphery of hyaline connective tissue forming the presumed valve cord No rheumatic granulomata or fibrinoid necrosis or anoxemic myocardial injury is detected There is minimal vascularization present

The appearance of this thickened mitral valve is well illustrated in Fig 4 *E* where it is apparent that the thickening is due to a plaque of collagenous tissue superimposed upon an otherwise normal mitral valve The collagen nature of this tissue was confirmed by Massons Trichrome stain It will be noticed how similar this valvular lesion is to the findings illustrated in Fig 3 and those in the carcinoid syndrome as illustrated in Fig 4 *F* and how different this lesion is from the

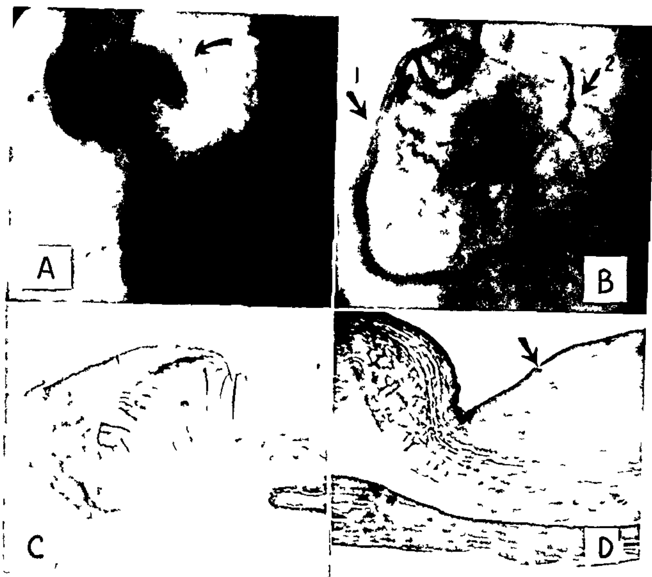


Fig 1 Patient No 43 *A* Angiogram revealing distortion of aortic valve and marked aortic regurgitation Arrow denotes area just beyond ostium of left coronary artery which is so narrow that the artery fills by retrograde flow only *B* Shows enlarged but otherwise normal right coronary artery (1) with retrograde filling of the left coronary artery (2) the ostium of which is constricted by fibrous tissue at the aortic root *C* Ball like mass of collagenous tissue in free margin of aortic valve cusp Dark linear streaks near the center are artifacts (folds in section) Elastic tissue stain (From Graham J R Fibrosis associated with methysergide therapy *in* Meyeler L and Peck H M Drug induced diseases vol 3 Fig 14 B p 265 Reproduced by permission of the publishers Excerpta Medica Foundation) *D* Plaque of collagenous tissue (arrow) superimposed on nearly normal aortic cusp Elastic tissue stain (Angiograms through the courtesy of the Department of Cardiology Cleveland Clinic Pathology specimens through the courtesy of Dr Donald Effler and Dr Beach Hazard Cleveland Clinic)

circumference at its ring and showed more thickening and fibrous tissue in its cusp than is usually seen

Patient No 45 A 40 year old female who took methysergide for migraine headaches from 1963 to April 1967 In May 1966 for the first time a systolic mitral murmur was noted and the patient was found to be in congestive heart failure In March 1967 the cardiac murmur had increased to Grade III over IV ' In April 1967 at open heart surgery a thickened mitral valve and chordae were removed and replaced by a Starr Edwards prosthesis The pathologic report on the valve and chordae reads as follows The valve has a glistening white surface on the ventricular aspect, but on the atrial aspect there is some roughening due to shallow pits and these are yellowish with slight injection of vessels The valve itself is thickened to 3 mm along the edge The upper ends of the chordae tendinae have been taken up into the valve and the lower or free portions now measure 1 cm in length These

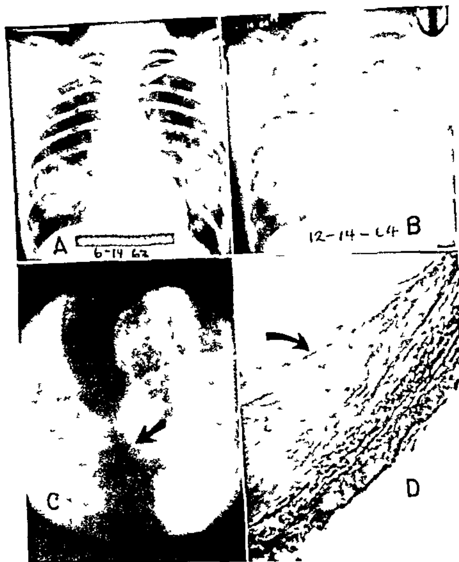


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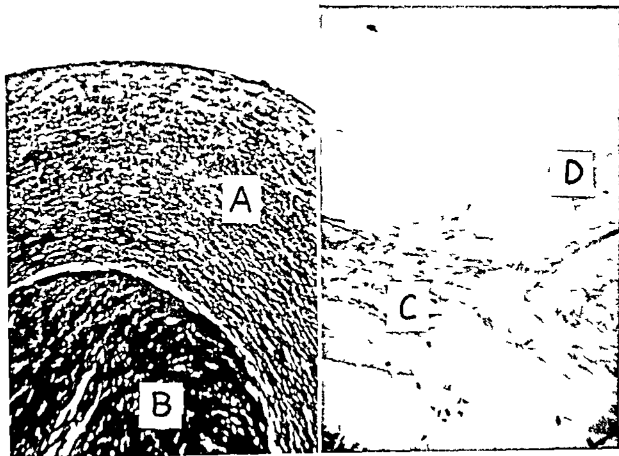


Fig 3 Patient No 15 Left uniform concentric ring of dense collagenous tissue (*a*) surrounding core (*b*) representing original chordae tendinae Right sheet of dense collagenous tissue (*d*) superimposed on mitral valve (*c*) (Left—from Graham J R *In*, Drug Induced Diseases Meyeler L and Peck H M editors Fig 14 C p 265 courtesy of Excerpta Medica Foundation Amsterdam Netherlands)

total disruption of the rheumatic valve (Fig 4 *D*) which is totally distorted by collagen tissue and calcification

Comment on pathology

The cardiac lesions described above in the four patients whose hearts have been examined are manifested mainly by involvement of the left side of the heart, except in one patient (Patient No 15) where the tricuspid valve was also slightly involved

Fibrotic thickening of the aortic and mitral valves chordae tendinae, tips of the papillary muscles, and to a slight extent, the endocardial surfaces of the left ventricle is noted In one patient (Patient No 43) the root of the aorta the aorta itself and the left coronary ostium were densely involved

The thickness was maximum at the free surface of the valves There was fusion and thickening of the chordae tendinae and mild 'white capping" of the papillary muscles due to the deposition of new fibrous tissue

Microscopic examination reveals the most interesting findings Grossly the appearance could pass for rheumatic endocardial involvement Under the microscope however major differences between rheumatic heart disease and that related to methysergide are noted In addition similarities to the pathology of the carcinoid syndrome are observed Some of the comparisons of the pathology in rheumatic heart disease the methysergide and carcinoid heart disease are illustrated in Fig 4

Although, in all three conditions the chordae tendinae are thickened and fused by the application of a fibrous plaque surrounding them, the valvular involvement is quite different in the rheumatic lesion from that found in the methysergide lesion and the latter turns out to be strikingly similar to the abnormal process involved in carcinoid heart disease

The rheumatic valvular deformity generally results from inflammation and scarring of the valve cusp itself by infiltration of the fibrocollagenous tissue within it In some cases the

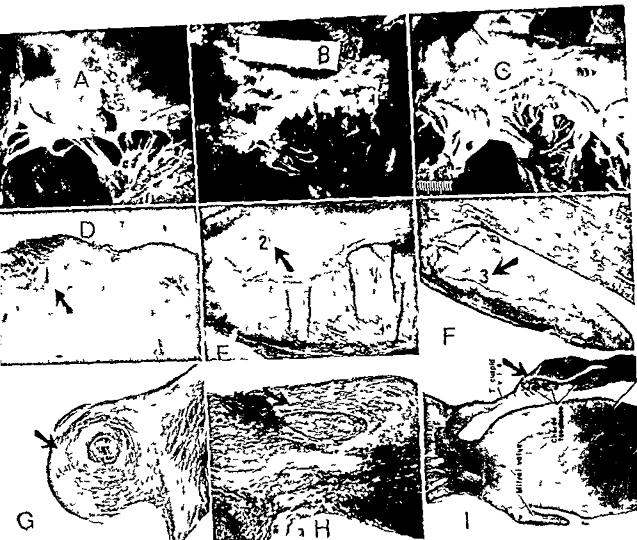


Fig 4 The top arrow (*A* *B* and *C*) reveals the similarity in appearance grossly of the mitral valves in rheumatic heart disease (*A*) methysergide induced heart disease (*B*) and carcinoid heart disease (C) The thickening of the valve itself and of the chordae and the white-capping of the papillary muscles all appear grossly similar The microscopic abnormalities however are distinctly different In *D* (rheumatic heart disease) may be seen the intrinsic disruption of valve structure by dense collagen and areas of calcification (1 arrow) whereas in *E* (methysergide induced heart disease) the microscopic section reveals a normal valve structure (Patient No 45) with a superimposed plaque of fibrous tissue (2 arrow) practically identical in appearance to the plaque (3 arrow) applied to an otherwise normal mitral valve in carcinoid heart disease (*F*) The microscopic pathology of the thickened chordae is similar in rheumatic (G) methysergide (*H*) and carcinoid (*I*) heart disease consisting of concentric rings of dense collagenous tissue surrounding the chordae (Figs *C* *F* and *I* are from W C Roberts and A. Sjoerdsma [11] courtesy of American Journal of Medicine Fig 4 *E*, courtesy of Dr D S Munroe and Fig 4 *H* from J R Graham [6] courtesy of Excerpta Medica Foundation Publishers Amsterdam Netherlands and Dr Clair E Basinger)

whole valve is replaced by dense nodular collagen with areas of calcification in the damaged tissue Vascularization within the substance of the valve cusp and within the endocardium is seen Aschoff bodies are characteristically present in the myocardium MacCallum patches are usually seen in the endocardial surface of the left auricle

Mast cells have been described in rheumatic heart disease but they are generally seen only near the regions of increased vascularity of the cusps.

In the methysergide induced lesions the valve structure itself is not affected and the grossly fibrotic and thickened appearance of the valve is

Table II Cardiac murmurs during methysergide treatment

Total no of patients studied	48
Patients with murmurs	47
Systolic murmur at apex	17
Systolic murmur at aortic area	5
Diastolic murmur at LBS and/or aortic area	6
Combination of systolic and diastolic murmurs	19
Total no of diastolic murmurs	25

found to be due to a layer of fresh collagen tissue placed on top of otherwise unharmed valve tissue

It is of interest that both grossly and microscopically, these findings are similar to the situation discovered in the valves affected by the carcinoid syndrome—even to the interesting detail of microscopic detection of many mast cells in the fibrous layer of the valves in these two conditions There was, however, no clinical evidence of the carcinoid syndrome in these patients In one case, urinary excretion of 5HIAA was measured and was normal

Roberts and Sjoerdsma[11] described the cardiac lesions in the carcinoid syndrome as a focal or diffuse collection of a peculiar type of fibrous tissue which was free of elastic fibers and which was desposited on the endocardium of the valvular cusps on the endocardium of the cardiac chambers, and on the intima of great veins, coronary sinuses and occasionally great arteries'

"The valvular cusp per se, remained normal as did the mural endocardium and each was clearly separated from the fibrosing process by the elastic membrane which covered its surface'

This description fits very closely with the type of lesions that are seen in the methysergide induced heart lesions

Although these lesions bear a striking microscopic resemblance to carcinoid heart disease it is important to point out that they are confined, for the most part, to the left side of the heart, whereas carcinoid heart disease is characterized most commonly, though not exclusively, by a right heart disorder

Although the lesions somewhat resembled the gross lesions seen in the African variety of subendomyocardial fibrosis,[12] they were easily distinguished by the absence of any subendocardial or myocardial lesions The microscopic characteristics of our cases also rule out bacterial, rheumatic, and nonbacterial thrombotic endocarditis by the absence of any destructive, highly cellular process leading to vegetation

Discussion

The difficulties inherent in drawing conclusions about the causal relation of drug therapy to the development of cardiac lesions are great there is always the possibility that the previous notations in records regarding the presence or absence of murmurs are inadequate, the chance exists that other causes for the murmurs may be operative even though not obvious at the time, different observers may make different observations and place different significance on the findings, murmurs may vary in intensity in relation to changing circulatory dynamics Conscientious efforts have been made in each case to verify records, duplicate observations, and explore possible etiologies other than methysergide Previous records were thoroughly checked for any reference to murmurs Previous history of rheumatic fever or other heart disease that would explain the murmurs under discussion was searched for and none found, and in the current records there was no evidence of rheumatic fever activity Repeated and duplicate observations were made of the murmurs in our patients by two different observers Murmurs rated as Grade 1/6 were included only if they were definite persistent, and 'organic in quality

Etiologic relationship

The reasons to suspect that methysergide is etiologically related to the appearance of these cardiac lesions are the following (1) A thorough search was made in each patient s past medical records for the existence of cardiac murmurs prior to the administration of methysergide None were found in the cases included in this series with two exceptions and in these patients, murmurs were not present when therapy was started (2) At the time the murmurs were first noticed during methysergide therapy there was no other known likely cause for their occurrence (3) The appearance of the murmurs is insidious If the drug is continued the murmur worsens

some patients even go on to develop cardiac decompensation (4) Some patients had regression of the cardiac murmurs or complete disappearance *after* methysergide was discontinued. It is unusual for murmurs to disappear over the course of a few months unless they are due to functional causes (e g anemia thyrotoxicosis acute cardiac dilation pulmonary embolism etc) none of which were operative in these patients (5) In the patients who came to surgery or autopsy the nature of the cardiac lesion was of an unusual type strongly similar in each case (6) Some of these patients acquired their murmurs while simultaneously developing retroperitoneal fibrosis a recognized complication of methysergide use Both the fibrotic disorders and murmurs gradually regressed after the drug was discontinued. (7) In our experience similar lesions have not been observed in over 300 patients since we instituted an interrupted regimen of methysergide administration

Two patients in this series developed both murmurs and pleuropulmonary fibrosis while on methysergide therapy Both conditions improved after methysergide was discontinued.

No one of these reasons in itself could offer conclusive evidence that methysergide is causally related to the development of the cardiac lesions The combined evidence of them all however certainly points in this direction It seems beyond the realm of coincidence that in previously murmur free patients currently suffering from no other cause for the development of murmurs such definite murmurs should have occurred only during methysergide therapy and that in many cases they regressed slowly after the drug was withdrawn In addition to this it is remarkable that in four patients in whom the valvular pathology could be studied, all the lesions were pathologically similar and of a special type quite distinctive from the more common conditions causing valve scarring

In view of all these findings it is reasonable to assume that methysergide therapy was in some way responsible for the development of these lesions

Incidence

From 1959 to 1970 about 1 5 million people have used methysergide Through our own studies and information submitted by other doctors

Table III Progress of murmurs (after stopping methysergide)

Patients showing	*Complete regression*	*Partial regression*	*No change*	*Worse*
Systolic murmurs	19	4	12	2
Diastolic murmurs	8	3	10	1
Cardiac surgery (tissue biopsies obtained)				3
Death due to cerebral hemorrhage (autopsy material obtained)				1
Death following cardiac surgery (noted above autopsy material obtained)				1
No follow up				2

we have reason to believe a causal relationship exists between methysergide therapy and the development of cardiac murmurs This link also appears to be strengthened through the reports of Dr Robert Kunkel of the Cleveland Clinic who has reported six such patients at the meeting of The American Association for the Study of Headache in Chicago June 20 1970 The pathologic changes in the heart valves of one of these cases in which examination became possible were similar to those described above[16]

From 1959 to 1966 methysergide was used by us on a continuous basis Our figures show that in our series of approximately 1 000 patients the incidence of cardiac murmurs during the continuous form of treatment from 1959 to 1966 was 3 6 per cent. Since then in the light of our experience with retroperitoneal fibrosis interrupted treatment has been used This consists of stopping the use of methysergide for a total of 1 to 4 weeks in each twelve month period. Since this change has been made no new case of fibrotic reaction has been recorded in over 300 cases.

The decline in the appearance of new cases with the beginning of interrupted therapy offers another argument that the drug is related to the development of these lesions A similar dramatically decreased incidence of drug induced retroperitoneal fibrosis as reported in the literature has been noted since interrupted therapy has been employed more widely

It should be emphasized however that (1) our patients are from referral centers for unusually severe headache problems (2) the patients themselves do not represent the overall type of popula

tion that takes this drug, and (3) in the earliest years of methysergide therapy, doses, at times well above currently accepted limits, were employed

Various theories have been postulated in the past regarding the possible mechanism of mode of action of methysergide to produce various fibrotic disorders The same theories could also be postulated for endocardial lesions under discussion [5,9,13] The exact mechanism is unknown But perhaps the most attractive theory is that, by virtue of its chemical structure which is closely related to that of serotonin this drug like serotonin causes direct stimulation of the growth of fibroblasts [14] Mitral tissue culture studies of the effect of methysergide on fibroblasts have not confirmed such an hypothesis [15]

Clinical implications

Since methysergide is currently the most effective prophylactic agent against migraine, its continued use seems justified in patients suffering from moderately severe forms of this malady in spite of its potentially severe side effects Contraindications to its use in addition to those usually noted (pregnancy, severe debility, vascular disease, and hepatic and renal disease) should also include valvular heart lesions, cardiac decompensation of any etiology, severe examples of "disorders of collagen,' and various fibrotic syndromes The only patients to be selected for this therapy should be those who can be relied upon to follow directions closely stop therapy periodically as indicated and report for regular check ups by the physician to detect early signs and symptoms of side effects

Interruptions in therapy may be individualized to fit the patient's life pattern but should consist of cessation of methysergide once or twice a year for a total period of four weeks Doses over 8 mg per day should be avoided Clear statements in the records should be maintained regarding the presence or absence of cardiac murmurs and auscultation of the great vessels of the extremities and the abdomen for bruits should be included in routine check ups In patients who have developed loud cardiac murmurs and functional disturbances which suggest a need for catheter study and even cardiac surgery it may be indicated to stop the drug and observe the progress for two to three months if possible before resorting to cardiac surgery

Patients who present with murmurs suggesting rheumatic heart disease, especially with absence of a history of rheumatic fever, should be carefully screened for methysergide induced lesions They should also be screened for the presence of serotonin producing tumors of the carcinoid type

If patients come to surgical intervention, it is important to examine the pathologic lesions of the heart valves carefully to differentiate them from those of rheumatic heart disease New light may be shed on the subject if portions of the valves are immediately frozen and subsequently examined by immunofluorescent techniques in an effort to determine whether antigen antibody reactions are taking place in the valves It would also be valuable if such lesions are discerned in a patient taking methysergide to save and freeze serum at the time lesions develop so that it can be compared with serum taken a few months later to determine possible changes in immunoglobulins

Gratitude is expressed to all the physicians who have sent data for this paper and to the staff of the Headache Research Foundation who participated in its production

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Fundamentals of clinical cardiology

Prosthetic cardiac pacers in community hospitals

A physician s experience

Otto Kahn, M D, F R C P (C), F A C P *
Los Angeles Calif

Human longevity is continually being extended and it is postulated that by 1980, 23 million Americans will be over 65 years of age (12 per cent of the population)[1] The medical profession must be well equipped to meet the challenges of geriatric diseases not only at the university level the center for research and teaching but at the community level the center for pragmatic medi cine

Since the use of the first totally implanted prosthetic endocardial pacing system in 1960 to 1963,[2,3] the indications[4] and the need for this form of therapy have markedly increased It is now estimated at over 60,000 patients per year,[5] and this number is expected to double within the next few years [5]

The procedure conceived nurtured and tested in the academic centers has now outstripped the facilities of these institutions with their limited resources who should possibly devote their energies to other yet unsolved problems In the 1980 s, with an ever increasing patient load and broadening indications for cardiac pacing the academic centers will be totally unable to meet the challenge effectively, and must therefore relinquish this duty to the well equipped com munity centers Perhaps the community physi cian can add much to decrease the mortality (1 to 3 per cent)[4] and even morbidity (35 per cent)[6] re ported in most academic centers A retrospective study was, therefore, undertaken which sum marizes one physician s experience over a 5 year period in two community hospitals in order to elucidate the problems with this relatively new modality of therapy The results of this study might encourage the academician to easily relin quish his present responsibility to the ' inter ested community physician

Materials and methods

Patient selection All fifty three patients in the study group were evaluated and treated per sonally by the author during the period of Jan 5, 1968 to March 3, 1973 (5 years and 2 months) Patients were referred through the usual com munity hospital route, primarily by progressive internists and a few up to date family practi tioners Before resorting to prosthetic endocar dial pacing all patients were first put on a rig orous medical treatment program consisting of anticholinergics and sympathomimetics How ever, this form of therapy had to be abandoned in most cases because of undesirable side effects in effective therapeutic results, tachyphylaxis and so forth Patients with reversible causes of the symptomatic dysrhythmias due to drugs, acute myocardial infarction and/or myocarditis were naturally excluded and treated medically with good results for the most part The average age of the patient population was 69 4 years (with a range of 21 to 96 years) (Table I) Thirty four pa tients were male and nineteen were female

Pulse generator/lead system Thirty per cent of the pulse generators implanted were of the asynchronous (fixed rate) type while 70 per cent were of the synchronous (ventricular inhibited) type (Table I) The average preset pacing rate of these units was 74 pulses per minute (range 62 to 82 p p m) Most of the synchronous units were set at an optimal rate at the time of implantation by means of the pulse generator s adjustable rate control Ninety per cent of the synchronous

* Attending Physician Los Angeles County General Hospital and In structor of Medicine (Cardiology) University of Southern California Los Angeles

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Reprint requests to Dr Otto Kahn 12441 Old River School Rd Downey Calif 90242

models* used by the author had this adjustable rate facility

During the last 18 months endocardial potentials were routinely measured when implanting the synchronous models to ensure that these potentials were of sufficient magnitude to inhibit the unit following a ventricular depolarization

The majority of the endocardial leads implanted were of the bipolar type (Table I) The threshold of ventricular capture was measured for each lead at the time of implantation and as reported by others[7] varied with the type of electrode used Average capture threshold was 0 89 milliamperes (ma) (range 0 1 to 2 ma)

The implantation procedure Implantation of the pulse generator and lead system was performed by the author in the x ray department of two community hospitals The endocardial transvenous approach was used exclusively All were performed under local anesthesia (1/2 per cent lidocaine)

A single small right oblique deltopectoral incision was made and the cephalic or lateral thoracic vein mobilized, isolated and cannulated with an endocardial electrode The electrode was next passed antegrade under direct (image intensification) fluoroscopy guidance into the right atrium

The preformed guide wire stylus was passed into the electrode and the electrode was manipulated into the apex of the right ventricle but not wedged until after the stylus had been completely removed. If there was some doubt as to possible coronary sinus placement the pacing electrode was passed into the pulmonary artery retracted again without the use of a stylus and then wedged in the apex of the right ventricle where thresholds and endocardial potentials were promptly measured A scalar electrocardiogram plus anterior posterior and lateral chest x rays were obtained at the operative site Resuscitation potentials were readily available but fortunately never utilized.

Antibiotics were liberally used systemically and the pulse generator pouch was flushed with a gram of antibiotic prior to closure with a pressure dressing Good hemostasis was obtained and the wound was not drained. Minimal if any discomfort was reported by these patients during and after the procedure

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Table I Materials

Number of patients	53
Sex Male	34
Female	19
Age Average	69 4
Range	21 96
Pacers used	
Fixed rate	30%
Demand (ventricular inhibited)	70%
Pacing rate	
Average	74 p p m
Range	62 82 p p m
Ventricular capture threshold	
Average	0 9 ma
Range	0 1 2 ma

Electrodes used

Type	Distal tip size	No used
Medtronic Model 5819 (bipolar)	2 2 mm	38
Medtronic Model 5816 (bipolar)	4 mm	11
Medtronic Model 5818 (bipolar)	3 2 mm	4
Cordis Model 9F (unipolar)	3 mm	3

Indications for pacing The indications for pacing varied as in Table II with some overlap due to many different dysrhythmias Most of the patient population had historical physical or laboratory evidence of chronic systemic disease (Table III) with a great deal of overlap A patient for instance would often have 3 to 5 concomitant diseases Reversible organ decompensation existed in some patients at the time of pacemaker implantation and necessitated an extended hospital stay for several patients. The average hospital stay however was six days with a range of three days to three weeks The majority of patients left the hospital taking some form of cardiac medication Digitalis was continued in 39 patients (73 6 per cent) diuretics in 21 (39 6 per cent) nitrates in 31 (58 4 per cent) and antidysrhythmics in 12 patients (22 6 per cent) (Table III)

Patient follow up Two to three weeks after prosthetic cardiac pacer implant all patients were referred back to their original physician for periodic monthly follow up The patients were instructed to take and record their pulse twice daily (once in the morning upon arising and again in the evening upon retiring) The pulse rates were shown to their physician at periodic monthly visits during which time a rhythm strip was also obtained. Primary attention was focused on the rate per unit time Patients were

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implant but were rather thought to be due to postsurgical treatment for other problems Necropsies were obtained in 14 (63 7 per cent) of the 22 deaths Of the 22 deaths in this group 13 were males and 9 were females the average age was 69 years Their average life span after im plant was 13 4 months. Most of this study group had their pulse generators replaced prophylac tically at 24 to 29 months At the time of this re port, 16 (30 per cent) have had the primary unit replaced once while 5 (9 5 per cent) have had the primary unit replaced twice

Both acute and chronic complications relative to the primary implant were noted in 15 patients (28 per cent) (Table VI) One late complication was fatal (Table VI) demonstrating a total mor tality of one patient (1 9 per cent) There were no fatalities due to the procedure or in the immedi ate postoperative period. No infections or elec trode dislocations occurred. No exit blocks were documented while monitoring the patient s car diac rhythm for 72 to 96 hours The most com mon complication was electrode perforation This most frequently occurred with the use of the 2 2 mm electrode—7F tip Medtronic No 5819 This electrode however had the added benefits of achieving a lower ventricular capture threshold, and perhaps a longer battery life Electrode per forations did not in any case develop significant hemopericardium. Asymptomatic friction rubs were audible in many patients but no fatality was experienced with treatment The single case of electrode fracture was in a unipolar unit A previously reported[10] case of run away pace maker was effectively treated. In this case how ever not until after the patient had experienced an acute cerebral hemispheric infarction ending fatally some three weeks later with pneumonia

Discussion

This study was accomplished solely by one in terested cardiologist who installed all the perma nent prosthetic endocardial pacemakers at the community level Transvenous endocardial elec trodes were employed exclusively because of the significantly lower mortality associated with this relatively simple procedure[11,12] and treatment by a cardiologist and not a thoracic surgeon The av erage age of this series is similar to others[13,14] as is the male/female ratio However it is the author s belief that this group contains one of the oldest patients ever treated by this modality

Table IV Medical versus surgical treatment of symptomatic cardiac dysrhythmias

Prosthetic pacer study			*Medical study*	
No of patients in study	53			100
No died in hospital	2	3 8%	35	35%
No died in first year			50	50%
No died in four years			80	80%
No died in five years	22	41 5%	?	
No died due to treatment	1	1 9%	?	
Cardiac deaths	8	15 1%	80	80%
Noncardiac deaths	14	26 4%	0	

This 96 year old athlete incidentally continues to enjoy an exceptionally active and productive life to this date

The equipment used has changed slightly over the 5 year period. The author now uses bipolar endocardial electrodes exclusively the size de pending on the central vein to be cannulated. Bipolar electrode usage has been the result of a unipolar electrode fracture (Cordis) in an earlier experience It is also felt that unipolar pacing mode grossly deforms ventricular complex mor phology with difficult rhythm interpretation sometimes With the advent of demand mode (ventricular inhibited) pacing in 1966 to 1968[15,16] these units were used exclusively as the pri mary unit due to the high percentage of chronic complete heart blocks reverting back to sinus rhythm (30 per cent)[17] with consequent competi tive rhythms and perhaps increased mortality On elective replacement of the primary pulse generator after 24 months however if the pa tient has been in a prosthetic paced rhythm with no competition during this time a fixed rate (asynchronous) pacer was employed for possible longer pulse generator longevity and better reliability The rate of the prosthetic pacer was usually set at time of implantation depending on the state of myocardium coronary artery dis ease valvular lesions etc Many of the more re cent pulse generator models contain a hys teresis feature for preservation of battery life Endocardial potentials utilizing limb Lead I have recently been routinely measured for de mand pacers to gauge effective pacer inhibition At the time of installation great pains were taken to achieve a low ventricular capture thres hold. The electrode was wedged feebly under a right ventricular apical trabecular muscle bun

Table II Indications for pacing

Symptoms	Per cent of total	Rhythms	No of Patients
1 Stokes Adams attacks	73 6		
		a Third degree heart block	28
		b Second degree heart block Mobitz Type II	9
		c Bifascicular block	
		right bundle branch + Lt Ant Sup Hemiblock	8
		right bundle branch + Lt Post Inf Hemiblock	1
		d. Tachybradydysrhythmia syndrome	7
2 Congestive heart failure	26 4		
		a Sinus bradycardia – ventricular irritability	7
		b Nodal bradycardia 40 to 50/min	7

Table III Concomitant diseases at time of implant

Organ	Disease	No. of Patients	Per cent of total
Heart	M I (previous)	33	62
	CHF (previous)	36	68
	Hypertension	21	39 6
	Cardiomyopathy (by history)		
	Rheumatic	13	24 5
	Diphtheritic	6	11 3
	Alcohol	11	20 8
	Muscular degenerative disease	4	7 5
Metabolic	Diabetes mellitus	26	49
	Gout	13	24 5
	Thyroid dysfunction	5	9 4
	CRST syndrome – (Scleroderma Variant)	1	2
CNS	Cerebrovascular occlusion infarction and/or insufficiency	23	43 4
Lung	Emphysema, pulmonary fibrosis	30	56 5
Kidney	Azotemia, renal insufficiency	20	37 8
Liver	Previous jaundice hepatomegaly compensated function	6	11 3
Legs	Peripheral vascular insufficiency	18	34
Bowel	Vascular insufficiency peptic ulceration, diverticulitis neoplasia	16	30

instructed to notify their physician if their peripheral pulse decreased by five beats per minute They or a responsible relative were also instructed in the use of "radioauscultation' a small inexpensive transistor AM radio tuned to 550 KC, placed over the pulse generator and monitored for audible clicks[8] At the same time a peripheral pulse was felt and synchrony between these two phenomena was duly noted This could also be audibly transmitted by ordinary telephone The patient was instructed to attend to skin care over the pulse generator and immediately report to his physician any unusual swelling erythema or ulceration

Results

The results of these patients followed over a 5 year period are compared to a similar group studied by Friedberg Donoso and Stein[9] (Table IV) Of the eight cardiac deaths in this particular study four died in refractory congestive heart failure three had recurrent myocardial infarction with consequent cardiac decompensation and one died of a hypostatic pneumonia secondary to an acute cerebral infarction caused by a run away pulse generator six months after implantation The 14 noncardiac deaths are tabulated in Table V The three cases of endocarditis were not attributed to the prosthetic pacemaker

Table VII Comparison of complications

No. of patients in series	Kahn 53	Imparato 130	Bernstein 112	Fishman 60
Displacement of electrode	0	20%	18%	33%
Fracture of electrode	1 9%	1 5%	2 7%	5%
Erosion of skin by electrode	0	4 6%	0	0
Perforation	9%	7%	7 1%	0
Trapped electrodes	0	9%	0	0
Malfunction pulse generator	1 9%	0	?	?
Skin erosion	1 9%	5%	2 7%	?
Infection	0	3%	6 2%	5%
Emboli	5 6%	?	4 5%	?
Septicemia	0	1 5%	1%	3 3%
Miscellaneous	0	0	9%	0
Total complications	28.2%	31 5%	56%	63%
No of surgical interventions	13 2% (7)	?	56% (63)	200% (122)
Mortality	1 9%	2%	4 5%	6 7%

the patients in this study did have syncope In some patients several dysrhythmias were noted, accounting for overlap on the reported rhythms in Table II Over 90 per cent of the patients however enjoyed a therapeutic response to treatment. Over 75 per cent of the patients needed cardiac medications on discharge The extent of concomitant multisystem disease as depicted in Table III explains the rather high over all 5 year mortality (41 5 per cent) The author assessed each patient in depth and independently diagnosed multisystem disease on the basis of historical interview supplemented with past records, physical examination and objective corroboratory laboratory tests Many patients had several disease entities (3 to 5) with borderline compensation In the event of gross decompensation the patient was supported by temporary pacing supplemented by aggressive medical treatment in order to evaluate reversibility of the decompensatory process In three patients a plateau of borderline compensation was reached and it was decided that they would probably rapidly decompensate if pacing was discontinued. It is also of interest to note that the diseases mentioned are very common for this age group (1) cardiovascular system—old myocardial infarction congestive heart failure hypertensive vascular disease and cardiomyopathy (2) central nervous system—cerebral hemispheric infarction organic mental syndrome (mild) and transient cerebral ischemic attacks (3) pulmonary system—pulmonary emphysema, pulmonary fibrosis and cor pulmonale (4) endocrine system—carbohydrate intolerance (diabetes) hypothyroidism and hyperthyroidism (5) renal system—nephrosclerosis and glomerulonephrosis (6) peripheral vascular system—intermittent claudication (7) neoplasia—carcinoma of cervix and leukemia, (8) gastrointestinal system—diverticulitis and ischemic enteropathy with eventual infarction and (9) metabolic hyperuricemia with clinical gout in some

The results of this study carried on at the community level seem very encouraging when compared with medical treatment (Table IV) and similar pacer studies from academic centers (Table VII)[11,13,18] As viewed in Table IV the total 5 year mortality compares favorably with the immediate in hospital mortality of a comparable medically treated group The 5 year mortality of this series followed by the family doctor without the aid of a pacer clinic,[22] was eight patients (15 1 per cent) due to irreversible cardiac disease Only one was due to a pacemaker (Table VI) The noncardiac deaths, as outlined in Table V were high at 14 patients (26 4 per cent) over the 5 year period but not unreasonably so in patients with severe multisystem disease (Table III) The earliest postimplant death was at one month in a diabetic patient with mild, chronic compensated uremia. In retrospect, patients with this amount of disease regardless of age should perhaps not be treated. It should be noted, however that this patient was symptomatic (syncope) and did improve minimally with temporary pacing The three cases of endocarditis cannot be attributed to pacer im

Table V Noncardiac deaths

No of patients	Months after implant	Cause
1 Renal failure	1	Uremia secondary to diabetic nephrosclerosis
2 Cerebral infarctions	8	Aspiration pneumonia secondary to old bilateral CVA s
	7	Hypostatic pneumonia secondary to recent CVA
2 Cor pulmonale	11	Pulmonary fibrosis and insufficiency—idiopathic
	12	Pulmonary fibrosis and insufficiency secondary to toxic gas inhalation World War I
3 Neoplasia	16	Myelogenous leukemia with septicemia
	16	Cancer of cervix with obstruction radiation
	12	Cancer of cervix with obstruction radiation
3 Endocarditis	5	Secondary to ileofemoral endarterectomy
	12	Secondary to transurethral prostatic resection
	48	Secondary to severe sacral decubiti in a paraplegic with diabetes mellitus
3 Gastrointestinal problems	1 5	Bowel infarction two days after implant and after digitalis three laparotomies for bowel resection after three recurrent bowel infarctions
	13	Gastrointestinal hemorrhage in a CRST syndrome (scleroderma variant)
	16	Perforated colonic diverticuli and septicemia

Table VI Pacer complications

No of patients	Complication	Treatment and outcome
Acute (10/53=18 8%)		
5	Perforations	Five interventions and three replacements
3	Emboli	One pulmonary resolved nonfatal Two systemic (arterial) (1) CVA *fatal* (familial cardiomyopathy) (1) Leg embolectomy nonfatal
1	Electrode fracture	Nonfatal replacement
1	Bowel infarction after digitalization	A total of three bowel infarctions with three laparotomies—eventually *fatal*
Chronic (5/53 = 9 4%)		
1	Run away pacer †	Replaced CVA *fatal* in three weeks—Pneumonia
1	Chronic CHB reverted to sinus rhythm with symptomatic competition in 6 months	Replaced by demand pulse generator
2	Gravitational dissection down tissue planes	Corrected with aid of a truss
1	Skin ulcer 13 months after implant	Surgical correction with good consequent healing

Cordis Unipolar
†Cordis Corporation (Ventricor)

dle The electrode, once wedged feebly was not advanced 2 to 3 cm as others have described[18] but rather was anchored securely at the venous entry site with interrupted silk sutures Utilizing this method no electrode displacement was experienced, contrary to many other reports that have placed this complication at 22 to 33 per cent[13 18] Local anesthetic was employed exclusively

With the advent of demand mode (synchronous) pulse generators fascicular blocks[19] and endocardial (His bundle) electrocardiography,[20] the rigid criteria for prosthetic cardiac pacing have broadened considerably over the past five years[21] This limited study demonstrates that trend (Table II) The progressive community physician's *modern* approach to this often lethal malady is at times criticized by the more skeptical conservative colleagues It is of interest to note, however that approximately 75 per cent of

terested physician at the community level over a period of 5 years and 2 months

The 5 year mortality rate was 41 5 per cent (15 1 per cent cardiogenic and 26 4 per cent non cardiogenic) A complication rate of 28 2 per cent with one fatality (1 9 per cent) due to a faulty pacemaker was experienced. These results compare favorably with a similar medically treated group who had an *immediate in hospital cardiogenic* mortality of 35 per cent Contrary to other reports premature battery depletion was not found in this series

This community study compares favorably to several university studies who report a complication rate of 63 per cent a mortality rate of 6 7 per cent versus 28 2 and 1 9 per cent respectively as experienced in this group This study indicates that community standards are equal to or superior to university standards in this particular mode of therapy

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plantation The patients died 5, 12, and 48 months post implantation after a probable transient bacteremia following endarterectomy, transurethral prostatic resection, and multiple sacral decubiti in a paraplegic diabetic, respectively Two of these cases had associated rheumatic valvular disease Their endocarditis was not limited to the right side as in a similar reported third case [24] Since these cases occurred, high doses of antibiotics have been recommended in all patients subjected to any form of surgery, including dental procedures Small bowel infarction two days after implantation in another patient cannot be considered a procedure mortality since the patient had diffuse vascular occlusive disease, a history compatible with abdominal angina, and was being digitalized (a known splanchnic vasoconstrictor) [25] Even after three separate laparotomies for recurrent bowel infarction a fatal result was inevitable some 1 5 months after the original implant.

Two systemic emboli occurred in other cases one to a cerebral hemisphere (which eventually proved fatal), and the other to a leg was followed by an uneventful embolectomy Neither of these cases could be secondary to the procedure, since one of these patients had a congenital cardiomyopathy, namely progressive muscular dystrophy, and therefore the systemic embolus can be considered part of the natural history of this disease [26] The leg embolus is unexplainable since no congestive heart failure (especially right sided, with possible patent foramen ovale), catheter perforation, bacterial endocarditis, or atrial septal defect was diagnosed prior to the procedure

The pacing complications incurred in this study have been high at 10 patients (18 8 per cent) in the acute phase and five patients (9 4 per cent) in the chronic phase, but compared very favorably with academic centers[11 13 18] who report a complication rate of 31 5, 56, and 63 per cent, respectively A comparison of the complications are tabulated in Table VII Premature battery depletion, prior to 24 months, which has been reported by others to occur in 50 per cent of the pulse generators[22] was not encountered in this study

Perforation of the endocardial electrode was the most common (9 per cent) complication in this reported group, but it occurred less frequently than reported in other studies (14 perforations in 9 patients [155 per cent]) [27] Most of the perforations occurred with the use of the 2 2 mm tip bipolar electrode * None, however, occurred with the use of the 4 mm tip electrode † although a higher threshold of ventricular capture was obtained with this electrode

No hemopericardium or tamponade was evident with perforation and no patients were anticoagulated in the acute phase Three of the five patients with perforation stopped pacing and required immediate exploration and retraction with re wedging of the electrode No acute dysrhythmias were encountered One patient was treated with a larger 4 mm tip electrode† since repeated perforation was encountered after retraction of the primary electrode All patients had an uneventful recovery The overall incidence of perforation according to Kennedy and co workers[28] is thought to be approximately 8 6 per cent—remarkably similar to this report The use of antibiotics as employed by Fishman and co workers[18] is to be recommended, with one further step that the author exclusively used, the technique of flushing 1 Gm of antibiotic in a 10 c c vehicle into the pulse generator pouch prior to closure with a pressure dressing Good hemostasis was uniformly achieved without electrocautery and the wound was not drained The procedure was accomplished exclusively in the x ray department by one physician under strict, aseptic conditions utilizing local anesthesia (1/2 per cent lidocaine) with the aid of image intensification fluoroscopy The right cephalic vein was utilized in over 60 per cent of the cases

As recommended by Fishman and co workers[18] age was not considered as a barrier to treatment. No primary infections were experienced under these less than ideal conditions

It would appear on the basis of this limited study in community hospitals that this relatively simple viable and highly gratifying procedure can be offered with a great deal of safety and effectiveness at the community level Indeed perhaps the "interested community physician [29] with the results as depicted in Table VII can improve this simple, therapeutic procedure appreciably

Summary

This report deals with 53 patients treated with prosthetic cardiac pacers solely by one in

*Medtronic Model No 5819
†Medtronic Model No 5816

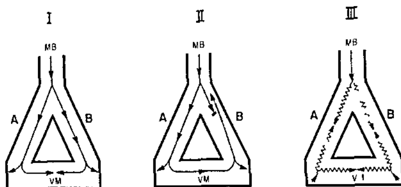


Fig 1 Diagram of a bundle of Purkinje fibers (*MB*) in the distal ventricular conducting system which divides into two branches (*A* and *B*) before making contact with ventricular muscle (*VM*) to form a loop *Panel I* shows the pathway of activation under normal conditions the impulse of sinus origin invades the main bundle (*MB*) leading to the loop conducts through both branches (*A* and *B*) into ventricular muscle collides and dies out *Panel II* shows the pattern of activation when an area of unidirectional conduction block is present (shaded area in branch *B*) conduction blocks in the antegrade direction (from *B* to *VM*) and not in the retrograde direction (from *VM* to *B*) but conduction velocity is normal. The impulse conducts around the loop too rapidly and returns to the main bundle (*MB*) before it has recovered excitability and therefore conduction is blocked in this refractory tissue *Panel III* demonstrates the sequence of activation when conduction is slowed in the loop but no region of unidirectional conduction block is present. The impulse conducts slowly from the main bundle through both branches However the ventricular muscle is activated earlier by impulses conducting from other regions where conduction is not depressed. These impulses collide with the slowly conducting impulses in *A* and *B* (Modified from Cranefield, P F Ventricular fibrillation, N Engl J Med. 289 732 1973 Reproduced by permission)

citability Re entry can result from this mechanism in fibers with fast response action potentials Finally, re entry may also occur as a result of focal re excitation due to inhomogeneous refractory periods in closely adjacent fibers This concept has been reviewed by Han [5]

II The slow response slow conduction and re entry in the ventricular specialized conducting system

Re entry due to slow conduction and unidirectional conduction block The anatomy of the ventricular specialized conducting system provides conduction pathways which are functionally suitable for re entry in the presence of slowed conduction Bundles of interconnecting Purkinje fibers are surrounded by connective tissue which separate them from ventricular myocardium In peripheral regions of the conducting system such Purkinje fiber bundles often arborize into many branches At sites where these Purkinje fiber branches make contact with ventricular muscle anatomical loops composed of the Purkinje fiber bundles and the muscle are often formed (Fig 1) Loops composed entirely of Purkinje fiber bundles in the peripheral ventricular conducting system also exist. Both unbranched bundles of interconnecting Purkinje fibers and the Purkinje fiber muscle loops can form re entrant pathways under the proper conditions A wide variety of ventricular arrhythmias result from re entry over these paths

Although re entrant arrhythmias sometimes occur in normal hearts they are usually the product of disease processes which alter the electrophysiological properties of cardiac fibers Purkinje fibers are fast fibers and normally generate fast response action potentials which conduct rapidly at a velocity of 1 to 4 M /sec Under normal circumstances, the rapidly conducting impulse of sinus origin will invade all the Purkinje fiber bundles of a distal loop and conduct into ventricular muscle where impulses will collide and die out because they are surrounded by refractory tissue (Fig 1 panel *I*) For re entry to occur in the distal ventricular specialized conducting system conduction must be slowed and a strategically located region of unidirectional conduction block must be present.

The mechanism whereby slowed conduction and unidirectional conduction block can result in re entry is illustrated in Fig 2*A* [6] In this distal loop composed of Purkinje fiber bundles and ventricular muscle an area of unidirectional conduction block is located near the origin of branch *B* impulses cannot conduct through this area in an

Electrophysiology and pharmacology of cardiac arrhythmias II Relationship of normal and abnormal electrical activity of cardiac fibers to the genesis of arrhythmias B Re-entry Section I

Andrew L Wit Ph D *
Michael R Rosen, M D *
Brian F Hoffman M D
New York N Y

I The concept of re entry

Under physiological conditions the conducting impulse dies out after sequential activation of the atria and ventricles because it is surrounded by recently excited and thus refractory tissue The heart then must await a new impulse normally arising in the sinus node, for subsequent activation The concept of re entry implies that the propagating impulse does not conduct throughout the heart and dies out after its complete activation but persists to re excite the heart after the end of the refractory period For this to happen the impulse must remain somewhere in the heart while the cardiac fibers it has excited regain excitability so that the impulse can re enter and reactivate them

The effective refractory period of human cardiac fibers is long and ranges from about 150 msec in the atrium to about 500 msec. in the ventricular specialized conducting system [1] The impulse destined to re enter or re excite the heart therefore must survive for this period if it is to outlast the refractory period [2] However it cannot remain stationary while awaiting the end of the refractory period but must continue to conduct over a pathway which is functionally isolated from the rest of the heart Such a conduction pathway must provide a return route to the regions which previously have been excited and must be sufficiently long to permit propagation of the impulse during the refractory period The cardiac impulse conducts at a velocity between 0 5 and 4 M /sec in cardiac fibers other than those in the sinus and atrioventricular nodes If it traveled at these speeds while waiting for the remainder of the heart to regain excitability it would have traveled in a pathway between 15 cm and 1 M long in order to survive [2] Cranefield and Hoffman[2] have stated that so long a path, however circuitous could exist in functional isolation from the rest of the heart has never seemed likely'

Travel at a normal velocity is not the only way in which the impulse, destined to re enter, might persist during the refractory period Slowing of the conduction velocity obviates the necessity of such a long conduction pathway For example if conduction is slowed to 0 02 M /sec the impulse would travel only 6 mm during a refractory period of 300 msec [2] Pathways of this length are readily available in the heart. Conduction is slow enough to enable re entry to occur in cardiac fibers with 'slow response action potentials— i e either in the normally slow fibers of the sinoatrial (SA) and atrioventricular (AV) nodes or in fibers whose normally fast response has been slowed by disease,[3,4] or other mechanisms such as drugs

Shortening of the refractory period also will facilitate the occurrence of re entry by reducing the period of time during which the impulse must linger in the heart, awaiting the recovery of ex

From the Department of Pharmacology College of Physicians and Surgeons Columbia University New York N Y 10032

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Reprint requests to Dr Michael R. Rosen Department of Pharmacology College of Physicians and Surgeons 630 W 168th St New York N Y 10032

Drs Wit and Rosen are Senior Investigators of the New York Heart Association Dr Rosen is a Research Fellow of the John Polachek Foundation Dr Wit is a Career Scientist of the Irma T Hirschl Trust.

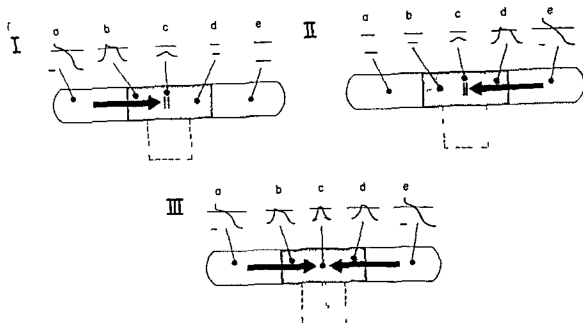


Fig 3 Summation in a bundle of Purkinje fibers Each panel shows a diagram of a Purkinje fiber bundle which has a depressed center segment indicated by the shaded area. A branch also arises from the center segment In *panel I*, when an impulse enters the bundle from the left it propagates into the depressed segment where conduction is blocked as indicated by the arrow Transmembrane potentials recorded during this event are shown above the diagram The action potential recorded from the unshaded area *(a)* which is not depressed appears normal The action potential recorded after the impulse enters the depressed center segment *(b)* arises from a reduced resting potential and has a low upstroke velocity and amplitude Only a low amplitude depolarization *(c)* is recorded at the region of conduction block where resting potential is low and transmembrane resting potentials without an action potential *(d* and *e)* are recorded from sites distal to this region of block The amplitude of depolarization of the response at *c* is too low to allow propagation out the branch. *Panel II* shows a similar sequence of events which occur when an impulse enters the bundle from the right end, propagates into the depressed area and blocks as indicated by the arrow Again, the amplitude of the response at *c* is too low to permit propagation out the branch *Panel III* shows the events when both ends of the bundles are excited and impulses conducted from both ends of the bundle toward the center as indicated by the arrows. Normal action potentials are recorded at *a* and *e* and action potentials arising from low resting potentials and with low upstroke velocities and amplitudes are recorded at *b* and *d* The impulses conducting from both ends of the bundle collide at *c*. As a result summation occurs the recorded response is *not* the low amplitude depolarization indicated by the *dotted trace* but rather an action potential of greater amplitude *(solid trace)* This summated impulse may propagate out the branch *(dotted arrow)* to re-excite the heart as a result of this increase in amplitude

product of disease processes Disease may convert fast fibers to slow fibers by reducing the membrane potential of the fast fibers thereby inactivating the strong inward Na current and the fast response[3,4] The mechanism for the slow inward current in these fibers is not inactivated and an action potential which is due entirely to the slow inward current remains These action potentials conduct at extremely low velocities of less than 0 1 M/sec and conduction is prone to block in a unidirectional manner[9]

If conduction in the loop of Purkinje fibers and ventricular muscle is slowed insufficiently to permit re entry or if a strategically located site of unidirectional conduction block is absent re entry still may be induced by premature activation[10] The normal impulse may spread through the Purkinje bundles and ventricular muscle in any of the manners indicated in Fig 1 If these Purkinje fibers are then reactivated prematurely before they have completely recovered excitability the premature impulse will conduct even more slowly and premature activation also may result in unidirectional block due to the lower safety margin for conduction in partially refractory tissue[10] Therefore slowed conduction and unidirectional block induced by premature activation can produce re entry as diagrammed in Fig 2A

Anatomically discrete loops of Purkinje fiber

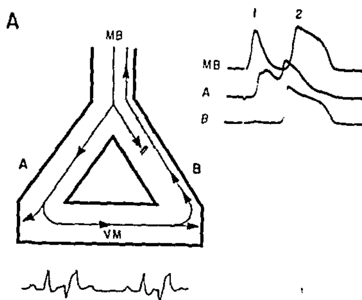


Fig 2A Sequence of activation of a loop of Purkinje fiber bundles (*A* and *B*) and ventricular muscle (*VM*) during re-entry A region of unidirectional conduction block is indicated by the darkly shaded area in branch *B* Conduction cannot occur through this area in the antegrade direction (from *B* to *VM*) but only in the retrograde direction (from *VM* to *B*) Slow conduction is present throughout the loop At the right action potentials recorded from a similar anatomical arrangement of canine Purkinje fibers are shown. Conduction in the loop was depressed with elevated K^+ and catecholamines Action potentials in the top trace were recorded from the main bundle leading into the loop (*MB*) The action potential in the middle trace was recorded from branch *A* and the action potential in the bottom trace from branch *B* Action potential *1* in *MB* results from antegrade propagation in this bundle the response in trace *A* was elicited as the impulse conducted through branch *A* and the action potential in *B* occurred as it propagated retrograde in this branch Action potential *2* in *MB* is the retrogradely conducting re entrant impulse The bottom of the figures shows a possible electrocardiographic pattern which may result from this type of re entry (see text for further discussion)

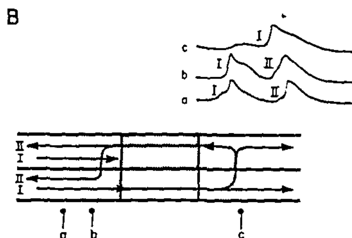


Fig 2B Diagrammatic representation of a possible pathway of impulse propagation during re entry by the mechanism of reflection in two parallel Purkinje fibers within an unbranched Purkinje fiber bundle A severely depressed area where unidirectional conduction block occurs is indicated by cross hatches and moderately depressed areas indicated by stipples An impulse (*I*) propagating through both fibers is completely blocked in the upper fiber at the area of unidirectional block but traverses the moderately depressed area in the lower fiber and then enters the upper fiber to travel in the reverse direction as impulse *II*. Above the diagram action potentials recorded from an unbranched bundle of canine Purkinje fibers during re entry by reflection are shown. Conduction has been depressed by elevated extracellular K^+ in combination with catecholamines *a*, *b* and *c* indicate the locations of the recording sites within the re entrant pathway shown in the diagram Action potentials labeled (*I*) were recorded during antegrade impulse conduction at sites *a* *b* and *c* as shown in the diagram Action potentials labeled (*II*) were recorded from the reflected or re entering impulse at sites *b* and *a* shown in the diagram

antegrade direction but can conduct retrograde As a result an impulse of sinus origin conducting into the loop through the main Purkinje fiber bundle blocks near the origin of branch *B* and only can enter branch *A* through which it conducts slowly into ventricular muscle This impulse then invades branch *B* in the retrograde direction This branch has not been excited previously and therefore the impulse can conduct retrograde in branch *B* through the region of unidirectional block to re excite the main bundle from which it originally entered the loop

Conduction around the loop must be slow enough to permit fibers in the main bundle to recover excitability the re entering impulse will block if it returns to the main bundle too rapidly while the fibers in this region are still effectively refractory (Fig 1, panel *II*) However, slow conduction without a region of unidirectional conduction block will not result in re entry (Fig 1, panel *III*) [7] The region of unidirectional conduction block is necessary to provide the return pathway for the re entering impulse by preventing part of the distal loop from being invaded by the antegradely conducting impulse

When the re entrant impulse has returned to the main bundle it also may reinvade the bundle of Purkinje fibers through which it originally conducted to the ventricular muscle (branch *A* in Fig 2) and again conduct back through the re entrant pathway This process may result in a continuous circling of the impulse around the loop or 'circus movement' [8] and repetitive excitation of the ventricles

The slow conduction and unidirectional conduction block which result in re entry may be a

depolarization phase may not be maximal and is dependent in part on the strength of the depolarizing stimulus[9,13] After a weak stimulus initiates an action potential with a submaximal amplitude further depolarization and an increase in amplitude can be evoked by the application of a second stimulus during the initial phases of the action potential[9] This results from activation of additional slow inward current. During the latter phase of repolarization and long after repolarization is completed this slow inward current becomes inactivated and the cell becomes refractory[9] The ability of two successive stimuli to evoke a response of greater amplitude than that caused by one stimulus is the phenomenon of summation[12] The two stimuli can be propagating action potentials as well as applied electrical pulses

When a segment of a *Purkinje fiber bundle* such as that shown in Fig 3 is markedly depressed, excitation of either end of the bundle may give rise to an action potential which will propagate to the depressed area and die out in that region (Fig 3 panels *I* and *II*) As it dies out the amplitude of the action potential progressively diminishes until propagation ceases (Fig 3) However excitation of both ends of the bundle simultaneously may result in summation of the low amplitude responses in the depressed segment giving rise to an action potential with a greater amplitude than either response alone in that region (Fig 3 panel *III*) The two low amplitude action potentials propagating from each end of the Purkinje fiber bundle will summate and increase the magnitude of the depolarizing current in the depressed region The resulting summated action potential cannot travel anywhere since both ends of the bundle are refractory as a result of the previous excitation However if a branch arises in the center of the depressed segment the activity evoked by summation can travel out the branch (Fig 3 panel *III*) This would be facilitated by an area of unidirectional conduction block in the branch so that conduction could procede only away from the depressed segment in the main bundle The process of summation is extremely slow and the summated action potential may not reach its peak level of depolarization for more than several hundred milliseconds after the summating impulses enter a depressed region Such a delay results from the slow conduction of the impulses into the region where summation occurs and the low rate of depolarization of the summated impulse Therefore propagation of the summated impulse out the branch may occur more than 300 msec after the summating impulses entered By this time the remainder of the branch and ventricles will have recovered excitability and the summated impulse will re enter the heart to cause an extrasystole[4,12] In order for re entry to occur by the process of summation a specific anatomical arrangement of Purkinje fiber bundles must be present whereby the summated impulse can propagate out through a branch to re excite the rest of the heart

Electrocardiographic correlates Re entry due to slow conduction and unidirectional block or slow conduction and summation can explain many electrocardiographic characteristics of ventricular arrhythmias Circus movement in loops of Purkinje fiber bundles or Purkinje fiber bundles and ventricular muscle is most likely to occur in the peripheral ventricular conducting system Likewise the anatomical arrangement of Purkinje fiber bundles necessary for summation may be more common in the peripheral Purkinje system Premature excitation arising by these mechanisms may result in widened, slurred QRS complexes However a depressed segment of an unbranched Purkinje fiber bundle capable of giving rise to re entry by reflection could be located anywhere in the A V conducting system from the His bundle to these distal peripheral Purkinje twigs If re entry of an impulse conducting from the atrium through the A V node occurred in the bundle of His by the mechanism of reflection it might appear in the electrocardiogram as a return atrial extrasystole or atrial echo (Fig 4*A*)[14] No premature ventricular activation would result from re entry by reflection of an impulse of atrial origin at this site If this depressed segment of the conducting system were located in an unbranched peripheral Purkinje fiber bundle re entry by reflection would result in a premature ventricular depolarization with an aberrant QRS complex (Fig 4*B*)

It is generally agreed that premature ventricular depolarizations which bear a fixed relationship to the preceding R wave (constant R R interval) are caused by the preceding impulse and may be re entrant[15] When re entry occurs by cir

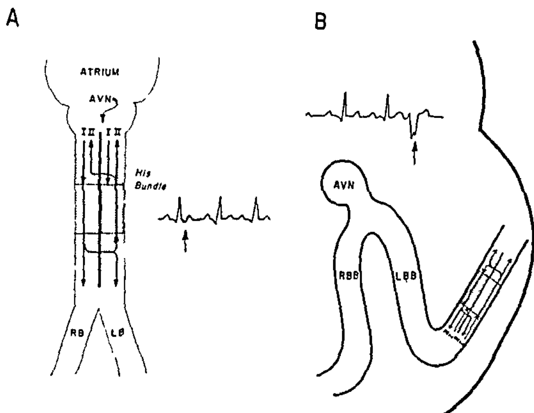


Fig 4 A and B Some electrocardiographic manifestations of re entry due to reflection In panel A the segment of depressed Purkinje fibers which was shown in Fig *2B* is located in the His bundle An impulse of atrial origin propagates through the AV node *(A VN)* and enters this depressed segment *(impulse I)* where re entry occurs by the mechanism described in Fig *2B* The reflected impulse *(II)* would return to reactivate the atrium as an atrial echo *(arrow* on the electrocardiographic tracing to the right of the diagram) In *panel B*, the segment of depressed Purkinje fibers is located in the peripheral conducting system Re entry occurs by the same mechanism but now the reflected impulse will reactivate the ventricles and a premature ventricular depolarization will occur as indicated on the electrocardiogram by the arrow

bundles are not the only areas of the ventricular conducting system where re entry can occur Re entry due to slow conduction and unidirectional block also can occur in unbranched Purkinje fiber bundles such as are found in the His bundle bundle branches, or peripheral Purkinje strands This mechanism for re entry was originally proposed by Schmitt and Erlanger[6] in 1928 and recently verified with microelectrode techniques [11] In such unbranched structures individual Purkinje fibers exist in a parallel arrangement, connected in some regions by lateral junctions of the sarcolemmal membranes (Fig 2B) Reduction of the membrane potential as a result of disease may not be uniform in such regions Therefore as shown in the diagram of parallel Purkinje fibers in Fig 2*B* the top fiber may be more depressed than the bottom fiber and there may be unidirectional conduction block in the top fiber *and only* slow conduction in the bottom one When a wave front propagates through this unbranched bundle the impulse will be blocked before entering the top fiber at the region of unidirectional block but will conduct slowly through the bottom fiber It then may enter the top fiber through appropriately placed lateral junctions and conduct both antegrade and retrograde By this mechanism called reflection [4] the impulse can re enter and re excite the unbranched bundle from the opposite direction and thereby re excite the heart

Re entry due to summation Re entry can occur by the process of *summation* in depressed cardiac fibers which have slow response action potentials [12] In normal Purkinje fibers with fast response action potentials the inward sodium current carrying system is maximally activated when threshold potential is reached and then inactivated Application of a second stimulus during the action potential will not evoke an additional response until the fiber has repolarized to about −55 mV In depressed cardiac fibers which demonstrate slow response action potentials the degree of activation of inward current during the

Annotations

Benign repetitive multifocal ectopic atrial tachycardia response to intracardiac atrial stimulation

In recent papers[1-4] on multifocal ectopic atrial tachycardia (also called chaotic atrial rhythm or mechanism) almost all the patients reported were elderly and usually severely ill with cor pulmonale ischemic heart disease cardiac failure diabetes or some combination of these factors. This has led to the belief that this arrhythmia heralds a very grave prognosis with mortality rates as high as 50 to 60 per cent[5] and that multifocal atrial tachycardia is almost always found in seriously ill elderly individuals [5]

It is worth noting therefore that a rare benign" variety of the arrhythmia does occur in young persons with otherwise normal hearts some of these patients followed over many years, have remained in excellent health apart from the persistent atrial irregularity [6] Cass[7] found eleven cases of repetitive atrial tachycardia with no demonstrable heart disease in the literature from 1900 to 1967

We studied a 30 year old woman in whom physical examination and full investigation revealed *no systemic or cardiac* abnormality except for multifocal repetitive atrial tachycardia she has kept well under observation for two years Thirty electrocardiograms recorded serially over this period invariably showed multifocal ectopic atrial tachycardia the criteria of which are [3] (1) two or more ectopic P waves with different configurations and with two or more different ectopic P P cycles (Figs 1 and 2) (2) atrial rate between 100 and 250 beats per minute (3) isoelectric line present between P P intervals and (4) frequent occurrence of varying P R intervals and A V block of varying degree (non conducted ectopic P waves)

No regular sinus rhythm was ever recorded. Runs of three to twelve ectopic P waves were separated by long pauses of varying duration, during which one or at most two presumably *sinus beats* (P waves of normal contour) or junctional escape beats usually occurred.

Pacing of the right atrium was attempted with a Philips *Electrodyne* T_3 fixed rate pacemaker from numerous atrial sites using currents up to 20 mA. at each site and pacing rates of 60 to 150 per minute From most sites no atrial response at all was elicited even during the long post tachycardia pauses (Fig 2) except for the high right atrium where strong stimulation did sometimes activate the atria

Most previous authors have assumed that the mecha

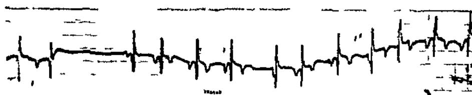


Fig 1 Esophageal lead showing varying P contour and varying P P and P R intervals

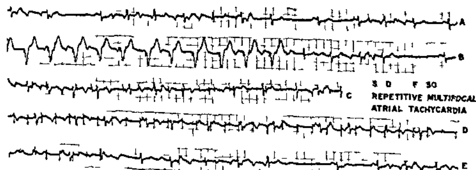


Fig 2 *Lead II* Strip A shows repetitive multifocal atrial tachycardia just before pacing Strip B shows the ventricles being paced for the first eleven beats after which pacing was switched off Strip C shows absence of atrial response to low right atrial stimulation Strips D and E show that high *right atrial* stimulation intermittently elicits an atrial response Pacing was terminated after the first few beats of Strip E.

cus movement or reflection, a sinus impulse activating the heart would result in the normal sequence of electrocardiographic events (P QRS T) While depolarizing the ventricles, and during inscription of the normal QRS complex the impulse would also enter the depressed segment in the re entrant pathway After depolarization of the ventricles the concealed impulse still would be conducting slowly in this pathway (during the Q T interval) Propagation in the depressed segment is electrocardiographically silent, most likely because the wave front is quite small and is conducted at very low velocities[15] When the impulse emerged from the re entrant pathway to re excite the heart, another often aberrant QRS complex would be inscribed (Fig 2A) Therefore the R R interval is determined largely by the time it takes the impulse to conduct through the re entrant pathway If the pathway is fixed in length and conduction through it always occurs at the same speed then the premature ventricular depolarizations should show fixed coupling to every normal QRS

Re entrant impulses resulting from summation also may be predicted to be characterized by fixed coupling in the electrocardiogram This is dependent on a constant conduction velocity of the summating impulses into the depressed segment and a constant conduction velocity of the summated impulse out the branch The time for summation also must be constant Any variability in these parameters would result in variable coupling intervals or disappearance of the re entrant impulses

Section II which will appear next month will include the entire bibliography for both Sections I and II

a possibility that the observed association is based on the selective early deaths of patients who drank lesser amounts of coffee There is a very small amount of published support for this possibility [6]

Another major criticism is that the observed association was obtained in a retrospective study many investigators argue that such studies are generally more subject to error than prospective studies such as the Framingham Study although that is an argument that may never be satisfactorily decided. Critics argue also that the coffee drinking habits of hospitalized patients may not reflect those of the nation as a whole that some of the Boston group s conclusions are drawn from a very small number of subjects—although the total number of myocardial infarction patients observed by the Boston group is three times as large as the number in the Framingham group—and that they have not taken into consideration the consumption of cola beverages which contain nearly as much caffeine as coffee or tea This last criticism in fact holds for all of the published studies considering the great increase in cola consumption in recent years it is possible that all of the studies may have produced spurious results In any event the unresolved contradictions in the studies the ubiquity of both coffee and cola consumption and the high incidence of heart disease in the United States suggest that further investigation is in order

Thomas H. Maugh, II Ph.D
American Association for the Advancement of Science
1515 Massachusetts Ave N W
Washington, D C. 20005

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The relative roles of diet and physical activity on blood lipids and obesity

While the importance of dietary factors in relation to blood lipids and obesity is generally accepted the role of physical activity in this regard appears less clearly established and indeed questioned [1 2]

Observations in Canadian Eskimos, comparing serum cholesterol and skinfold measurements in men from hunting camps and larger settlements in different age groups suggest that vigorous and sustained physical activity may actually outweigh dietary factors

Dietary patterns change drastically when Eskimos move from isolated hunting camps where meat and fish and small amounts of fat comprise the bulk of the diet to larger settlements where imported food, mainly staples such as flour sugar and lard, supplemented by some imported meat and some locally obtained fish and meat is consumed. Individual dietary patterns show less stratification and individual variation within a given native community than would be expected in a modern Western society thanks to persistence of native sharing habits and are essentially the same for young and old men.

Physical activity on the other hand, changes a great deal in various age groups in the hunting camps and much less for the settled Eskimos

Men from 18 to 39 are traditionally restless hunters almost constantly on the move This falls markedly off in the age group 40 to 54 and little more than fixing sleds nets and tools is done by camp Eskimos 55 years and older and they become more or less sendentary In larger settlements, where

Table I Serum cholesterol levels* in Canadian Eskimo men according to age group and way of life

Way of life	*18 to 39 years*		*40 to 54 years*		*55 years and over*	
	No	*Mean ± S D*	*No*	*Mean ± S.D*	*No*	*Mean ± S.D*
Living in hunting camps	33	155 8 ± 28 2	12	207 9 ± 43 0	9	216 6 ± 45 7
Living in urbanized centers or large trading settlements	21	217 6 ± 54 6†	12	238 3 ± 100 2	18	203 3 ± 48 6

*Similar trends seen in other blood lipid levels but with lesser degrees of significance
†Significant at P < 0 001

nism of multifocal atrial tachycardia is the same as that of ordinary unifocal atrial tachycardia except that there is more than one atrial ectopic focus in the former [5] If this were true one would expect the atria to be unremittingly activated by one or another of the ectopic atrial foci But in our patient as well as in others with benign repetitive multifocal atrial tachycardia [6 8] there were long pauses after every run of ectopic tachycardia during which one or two sinus escape beats usually occurred

Much evidence has recently been presented indicating that the mechanism of ordinary unifocal paroxysmal atrial tachycardia in most if not all cases is a re entry pathway passing through the A V junction [9] We suggest that in the benign multifocal repetitive variety of ectopic atrial tachycardia the re entry circuit varies in duration as well as in its precise anatomic course from beat to beat because of areas of impaired conduction in the atria Such refractory areas were demonstrated in our patient in whom ventricular pacing with far weaker currents (5 mA) invariably captured the ventricles continuously

This hypothesis would explain the varying P contour the varying P P intervals and the presence of first and second degree A V block (possibly A V block at the atrial level[10]) The fact that the ectopic tachycardia though always present terminates spontaneously every few seconds could be explained if one postulates a re entry circuit that after a few circuits becomes blocked when it encounters a refractory atrial myocardium

I A D'Cruz M D
A B Mehta M D
P N Kelkar M D
D B Pahlajani, M D
Department of Medicine
Lokmanya Tilak Municipal General Hospital
Sion, Bombay-400 022 India

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Coffee and myocardial infarction

Coffee and tea have frequently been suggested as factors that might increase the risk of heart disease because of the pharmacologic properties of the caffeine found in both Several studies of the risk factors for heart disease have produced conflicting results about the effects of the two beverages although the largest prospective study the Framingham Heart Disease Epidemiology Study [1] found no link between coffee and heart disease Two recent retrospective studies by the Boston *Collaborative Drug Surveillance Program* [2 4] however suggest that there may indeed be a strong correlation between coffee consumption and myocardial infarction

In two separate studies the Boston group compared a total of 716 patients hospitalized for myocardial infarction with control groups consisting of 13 423 patients hospitalized for other reasons They concluded that patients who drank one to five cups of coffee daily ran an approximately 50 per cent greater risk of developing myocardial infarction than did those who drank no coffee and that those who drank six or more cups per day ran about a 110 per cent greater risk. They found no association between coffee consumption and any other type of heart or other disease Interestingly they also found no association between tea consumption and any disease suggesting that caffeine is not the source of the observed association Also interestingly they found a strong correlation between coffee consumption and cigarette smoking but only a slightly increased risk of infarction associated with smoking and a lesser over all risk associated with smoking than with coffee

The Boston group s results have provoked much skepticism [6] especially since they contradict the Framingham study The major reservation is that their study necessarily excludes a large class of subjects. As many as 60 percent of myocardial infarction victims die before they reach the hospital and as many as 30 per cent of the remainder die within 72 hours of admission Since interviews for the Boston study were conducted more than 72 hours after admission there is

nurses and attendants the meaning of this order The physician must in turn carefully indicate the care he wishes for his patient and why This can be done without difficulty and with an extremely favorable response from all attendants if they are approached properly and if justification is made known. When private nurses are employed, the order to discontinue hospital routine is more readily achieved if the physician will only devote the necessary time to explain to the nurses the reasons for the instructions and objectives in therapy The type of diet must be explicitly ordered. Unless attention is directed to "Hospital Routine the patient his family and physician will soon realize that the hospital can be less than an adequate place for the care of the seriously sick heart patient

G E. Burch, M D
Charity Hospital
New Orleans La.

Table II Triceps skinfold thickness* in young and elderly eastern arctic Eskimo (1964) comparing men from large settlements in Hudson Strait (living mainly off handicraft manufacture and welfare) and North Baffin Island hunting camps

	18 to 49 years		50 years and over	
	No	Mean ± S D	No	Mean ± S.D
North Baffin hunting camps and small settlements	88	5 07 ± 0 85	23	7 24 ± 2 18
Hudson Strait settlement pre dominantly living off handicraft and welfare	17	† 8 12 ± 3 34	6	6 02 ± 3 76

Similar trends seen in other skinfold measurements but with slightly lesser degrees of significance
†$P < 0.001$

the majority are wage employed or live on welfare or by handicraft manufacture much less difference in physical activity between the various age groups is seen

This background information may help to explain our findings in regard to serum cholesterol (Table I) and skinfold measurements (Table II) in various age groups of Eskimo men living in hunting camps and large settlements

The physically most active younger Eskimo men had very *significantly* lower serum cholesterol and much thinner skinfolds than their opposite number in the larger settlements while differences dwindled in the middle age group and reversed (although not significantly so) in the elderly men from both groups

Observations of low serum cholesterol and other blood lipids and corresponding thin skinfolds in active Eskimo hunters and other physically very active population groups such as the Bushmen and Masai[3,4] with quite different and partly even very fat and cholesterol rich diets[4] may have to be considered when discussing the relative role of diet and physical activity in our own extremely sedentary Western societies where differences in physical activity between active and inactive life styles may be quite small compared to less sophisticated societies

Dietary adjustments certainly appear to offer to a majority of our society more easily achieved and therefore probably more practical solutions That however even in our society physical activity if exercised long and severe enough brings a reduction in blood lipids was demonstrated by Lopez and associates[5]

O Schaefer MD
Northern Medical Research Unit
Medical Services
c/o Charles Camsell Hospital
12815 115 Ave.
Edmonton, Alberta, Canada

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Hospital routine and the heart patient

A hospital operates with principles and practices designed to meet most effectively the needs of the average patient But, seriously ill patients are *not* average Therefore in the management of patients with serious heart disease the routine practices should be suspended temporarily For example as a routine early each morning the patient s room is cleaned the water at the bedside is changed the commode is emptied temperature and pulse and respiratory rates are obtained, bed clothing is changed medication is administered blood urine and/or stools are collected the food tray is delivered noises are produced in the corridor and many other annoyances are introduced which not only awaken and disturb the seriously ill patient who needs rest but often anger him The physician s orders for special studies such as roentgenograms electrocardiograms and others, are fulfilled. Patients admitted for care and rest *therefore should be immediately removed from* Hospital Routine This is done by writing as the initial order *Discontinue all hospital routine* (this includes discontinuing the routine diet) followed by a direct and careful explanation to the chief nurse and other

should have mentioned that several episodes of competition were detected by the pacemaker service and we were notified immediately We merely wish to point out that certain events such as the atrial flutter episode could have been misinterpreted by recordings not demonstrating atrial activity We still use the Cardiac Data Corp Testing Service extensively since we feel that the 24 hour availability of expert interpretation of pacemaker problems is valuable

William H. Carter M.D
3101 MacCorkle Ave. S.E.
Charleston, W Va. 25304

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The cause of arterial disease

To the Editor

We were interested to read the article by Dr Stanton in the June 1974 issue of the JOURNAL entitled, "The cause of arterial disease The author mentions that the first clinical description of coronary heart attack was made in 1912 We think that it would be interesting to mention one controversial case history from The Bible [1] A man called Nabal described as a heavy eater and drinker with a harsh temper came to a serious conflict with King David. Nabal s wife by her charm and a large amount of money was able to please King David When the miser Nabal was told by his wife about the money she paid to David, his heart died within him and it became as a stone ten days after he died. [1]

The prominent medical historian J O Leibowitz[2] suggests that Nabal had a cardiac infarction following the anxiety and great fear of King David. In this case death overcame him after ten days of great tension perhaps as the result of a second and fatal heart attack."[2]

Moshe Steier M D
Assistant Professor
Department of Pediatrics
New York Medical College
New York N Y 10029

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Reply

To the Editor

When I read the letter from Dr Moshe Steier you so kindly sent on to me which was a comment on my annotation, "The cause of arterial disease " I wondered whether both you and your readers would perhaps not recognize that this is a leg pull, behind which perhaps is an attempt to criticize my annotation by inferring that it is not worth serious comment.

However let us take Dr Steier seriously and insist that anyone questioning whether heart attacks were known before 1912 must accept that such dramatic medical events must have been evident to such physicians as Sir William Osler who failed to mention them in his 1900 lectures and to Paul Dudley White perhaps the greatest cardiologist of this century who did not see his first case before 1926 at a time when he was already established in his specialty

No one doubts that heart attacks can arise from different causes Syphilis can bring about a pathology that includes aneurysm and aortic stenosis, both causes of sudden death. This can arise also from anemia However the cause of the heart attacks which bring about the sudden death of 500 000 people per annum in the U.S A is a completely new phenomenon and, in my view *no occasion for levity*

Now to the case of Nabal and his anxiety and great fear It has been well documented that in primitive peoples where the basis for their beliefs and mores is in ignorance and superstition, susceptible persons can die of fright usually as a result of being put under a spell or fetish. Indeed I had one such case in my bush hospital in the Congo where my own chauffeur was put under a curse by a father who alleged he had killed his child in hospital by black magic and was brought in to me in a state of complete collapse with a heart in fibrillation which was relieved only by external cardiac massage and intravenous pentothal And I would suggest that Nabal died of fright the underlying pathology being a vaso vagal effect

However it is the most difficult problem of all to get people to change their established opinions *We believe (that is,* the members of the McCarrison Society in England) that cardiovascular disease due to atheroma is a new phenomenon, due to a drastic change in diet since 1875 that this change essentially is the introduction of sugar and white flour and that the basis of the damage to the arterial wall permitting deposition of lipid is chlorine dioxide in tap water and white bread CO in the blood from cigarettes and vitamin C lack allowing damage to lining tissues However we recognize the difficulties *pioneers always* meet when confronted with the conventional wisdom which will always ally itself with commercial interests.

Dr G A Stanton
The Survery
Marshland St.
Terrington St Clement
King's Lynn Norfolk
England

Opening or closing snap of mitral valve

To the Editor

A controversy regarding the mechanism of the snap of the mitral valves in mitral stenosis and other conditions has recently appeared in the JOURNAL. My position based on an extensive literature survey and on our catheterization data led me to conclude that the opening snap is generated when the velocity of the stream between the partially opened leaflets of the valves g nerates a local negative pressure and

Letters to the Editor

Coronary sinus pacemaker problems

To the Editor

The article by Bowman and Carter in the JOURNAL (87 507 1974) leaves the readers with the impression that the coronary sinus pacemaker was pacing correctly and that pacemaker malfunction was not present I am particularly concerned about the unusual behavior of this coronary sinus pacemaker electrode which alternately paced atria and ventricles and at times failed to sense ventricular activation as seen in Fig 5A Most alarming was failure to return the ventricular cycle during long periods of asystole which in this strip approached 1 7 seconds

Several real and philosophical problems emerge from this series of electrocardiograms The first and probably most important is that the patient is not protected from asystole as seen in Fig 5A Second competition or arrival of the pacemaker spike in the vulnerable period of the ventricle cannot be prevented, and consequently fatal ventricular arrhythmias particularly in the face of an acute process, could occur Third during atrial pacing A V block may occur particularly if the patient is placed on antiarrhythmic drugs The physician who inserted this unit would be in legal jeopardy if he did not measure A V conduction time and the integrity of the A V transmission system before he implanted an atrial pacemaker Futhermore he would be in legal jeopardy certainly because of the inappropriate alternation of atrial and ventricular pacing as well as the malfunction of the pacemaker electrode system as seen in Fig 5A Once a malfunction is identified it is incumbent upon the attending physician to immediately take measures to correct this problem Any catastrophe that may follow after the identification of pacer malfunction could be attributed to the pacer malfunction although it could result from other systemic medial problems In this instance I feel that the patient has been done a disservice by failure to properly place the electrode leads for adequate sensing and capture at all times

The central issue of this article was the apparent failure of the telephonic monitoring system to alert the attending physicians to the fact that the pacing system was not functioning correctly The alternation in the spike pulse interval probably resulted from alternation between atrial and ventricular pacing The fact that the physician was warned of a malfunction should have led to a more in depth investigation of the problem and, in this instance correction of this malfunction should have been effected immediately

Leonard S. Dreifus M D
Professor of Medicine
Jefferson Medical College
Chief Cardiopulmonary Department
The Lankenau Hospital
Philadelphia, Pa. 19151

Reply

To the Editor

Dr Dreifus has expressed appropriate concern over three potential problems that could occur with the present coronary sinus pacemaker in this patient We also were concerned with these problems but elected not to replace the pacemaker for reasons that should have been discussed in this paper

1 Concern was expressed over the lack of protection from asystole occurring during an episode of atrial flutter We felt that the risk of asystolic death was extremely remote for the following reasons (a) The patient s sinus bradycardia had never caused syncope but rather weak dizzy spells, proved by telemetry to occur with sinus bradycardia The pacemaker was inserted in this 78 year-old woman for symptomatic relief of symptoms related to sinus bradycardia for which it proved effective Since there is yet no agreement that the patients with the sick sinus syndrome have an increased instance of sudden death over that of this general elderly population[1] (which of course is fairly high) we thought the relief of symptoms should be the main therapeutic goal (b) The atrial flutter which inhibited the pacemaker occurred only after one year and was easily controlled by quinidine For this event to cause death would require that the atrial flutter recur that the pacemaker not function every two to three beats as a ventricular pacemaker and that she not conduct on her own at a rate fast enough to sustain life (one recurrence of atrial flutter while on a lower dose of digoxin and a low dose of quinidine resulted in a faster ventricular response)

2 Competition was detected only twice despite numerous checks by the Cardiac Data Corp Testing Service While certainly today we prefer a demand pacemaker in such patients fixed rate pacemakers were used successfully for years with competition occurring in many patients literally millions of times without evidence that such competition caused an increased mortality rate In fact one series reported no statistical difference in mortality rates in patients with either type of pacemaker used in a setting of acute myocardial infarction[2] (We do not of course recommend fixed rate pacemakers under such circumstances)

3 At present His bundle measurements are routinely made by us before atrial pacemakers are inserted however at the time of the pacemaker insertion in 1971 this was not a routine procedure in our hospital At present there is no evidence that survival of patients with H V prolongation in the absence of syncope is increased by ventricular pacing Certainly we do not perform His bundle measurements in patients with conduction disturbance before using quinidine

For the above reasons we feel that the risk of replacement of the pacing wire that had relieved the bradycardia symptoms was greater than the risk voiced by Dr Dreifus Insertion of a ventricular endocardial pacemaker still involves a reasonable chance of both early and late complications[3] Late removal of a patient s pacing wire which we considered when the patient developed atrial flutter after one year probably represents an even greater hazard due to the endothelialization and clot formation which may occur on the catheter

Dr Dreifus felt that the essential issue of our article was to point out apparent failure of the telephone monitoring system to alert physicians to pacemaker malfunctions We

Book reviews

✓ **Physiology of the kidney** By Lawrence P Sullivan, Ph.D., Philadelphia 1974 Lea & Febiger Publishers, 149 pp $6 50 (soft cover)

This excellent book designed for teaching renal function to students and doctors is highly recommended. Sullivan has correlated gross and ultrastructural anatomy with renal function. The relationship of blood flow and the spatial arrangements of the blood vessels to renal function are well illustrated and discussed. Chapters include such subjects as renal transport of organic or inorganic substances, tubular function, countercurrent flow diuresis measurements of renal function, and other aspects of renal physiology This small book is worth owning and certainly studying by students and physicians for a brief review of renal physiology

Cardoneumologia Fisiopatologica y Clinica By Ignacio Chavez Rivera published by the Universidad Nacional Autonoma de Mexico Facultad de Medicina, Mexico D F 1973 2 vols

This two volume textbook of about 2 000 pages on pathologic and clinical cardiopulmonary diseases by Prof. Ignacio Chavez Rivera is a thorough review of the problems any clinician will encounter in practice of cardiology The two volumes include an interesting history of cardiopulmonary medicine anatomy training the peripheral and microcirculation, electrocardiography vectorcardiography metabolism pathology disease states, physiologic disturbances such as coma and syncope hemodynamic phenomenon (normal and abnormal) the arrhythmias, and many other cardiac and pulmonary problems. This is an excellent set of books. Prof Chavez has produced an excellent two-volume publication These volumes represent extensive effort and a fine result. Unfortunately it is in Spanish only but English and other language translations should appear soon. The volumes are highly recommended.

Nomenclature and criteria for diagnosis of diseases of the heart and great blood vessels The Criteria Committee of the New York Heart Association, Boston, 1973 Little Brown & Company 363 pp Price paper $5 95 cloth, $8 95

The booklet of the New York Heart Association entitled *Nomenclature and criteria for the diagnosis of diseases of the heart and great vessels* has been one of the most useful publications in cardiology for many years. Its greatest virtue has been the practical bedside clinical orientation of the presentations It has emphasized clinical logic Undergraduate medical students, interns, residents, fellows and all doctors have learned a great deal of cardiology from previous editions of this publication. But this seventh edition apparently like many other aspects of medicine has succumbed somewhat to procedures and gadgetry Surely patients with serious heart disease may be free from symptoms or even signs at the bedside, but this does not necessarily mean that the cardiac function as defined in previous editions of this book should not be considered useful and clinically accurate In fact, it is the function of the "pump" that really matters and previous experience has shown the functional classification to be most useful and certainly clinically reliable It is not possible to determine prognosis satisfactorily without some idea of cardiac function. But, cardiac function can be estimated adequately for clinical purposes at the bedside It is the impression of this reviewer that many physicians consider that too much time is required to talk to patients in order to determine function. Cardiac catheterization, with the poor fidelity of the methods as used in most centers, even with fancy exercise tests will never replace a careful history and physical examination of the patient by an expert clinician.

The decision to eliminate the peripheral vascular portion of this publication is acceptable Few physicians paid much attention to it, anyway The elimination of the therapeutic classification is all right but this reviewer though slow in employing it, has since found it useful in most patients.

Harold B Pardee nutured this publication for many years and was primarily responsible for the original publication and its great success. The seventh edition is a good reason for all of us in cardiology to miss Dr Pardee The original concepts of the book seem to be dying

This reviewer would suggest that all physicians continue to use the sixth edition and that the Committee reconsider its decisions and change this new edition Finally it seems noteworthy that even the sophisticated binding and appearance of the previous publications have been lost in this new edition

The heart Edited by Jesse E. Edwards M.D et al. Baltimore 1974 The William & Wilkins Company

Edwards and Lev edited a useful book on the heart in which cardiac pathology is nicely related to clinical manifestations of heart disease The illustrations and text describe concisely the fundamental pathologic changes encountered in clinical cardiology The considerations are limited to the common diseases both acquired and congenital The diagrams are particularly good and instructive Medical students, house staff and fellows as well as practicing physicians, will appreciate this book on fundamental aspects of practical cardiac pathology This is a valuable publication.

7TH European Conference on Microcirculation Aberdeen 1972 Part I Methodology in microcirculation Edited by J Ditzel and D H. Lewis, Basel, 1973 S Karger AG

This book contains the proceedings of the 7th Conference on Microcirculation. Like the previous conferences, this seventh must have been an excellent one Its importance is further appreciated when it is realized that the small blood and lymphatic vessels receive insufficient considerations in research and clinical medicine at present. This book contains several reports on methods rheology myocardial blood flow light microscopy ultrastructure clinical aspects clinical biomicroscopy and general miscellaneous considerations This is an excellent and highly recommended publication, rich with interesting and important information

Angiotensin Edited by Irvine H Page and F Merlin Bumpus New York, 1974 Springer Verlag 591 pp

This monograph on angiotensin edited by Page and Bumpus with the assistance of numerous contributors is an authoritative and fairly complete summary of the history chemistry and action of angiotensin. This polypeptide is con

causes the leaflets momentarily to snap shut before opening fully[1,3]

In the monograph *Ultrasound in the diagnosis of cardiovascular pulmonary disease* (C R Joyner Editor Year Book Medical Publishers Inc Chicago 1974) E Craige and N J Fortuin present data on the *Genesis of heart sounds and murmurs as demonstrated by echocardiography* (Chap 7 p 119 132) They state that the opening snap is indeed an *opening snap and not a closing snap that this is clearly demonstrable by phonoechocardiography* and that the opening snap occurs precisely at the moment when the rapid anterior opening motion of the mitral valve is abruptly checked

Inspection of Fig 7 3 (p 123) shows clearly in the four beats presented that the anterior mitral valve leaflet begins to move into the opening position during the registration of the second heart sound. Approximately 70 msec later the echo of the anterior mitral leaflet abruptly moves into a position of closure for a few milliseconds The recording of the snap is coincident with the nadir of the closing movement of the valve leaflet This striking demonstration of the simultaneity of the completion of the motion of transient closure of the valve leaflet with the onset of the snap appears to be strong support for the concept that the snap is actually due to a momentary *closure* and not due to opening

In Fig 7 5 (pg 126) showing a snap from a nonstenotic mitral valve the opening movements of the leaflet are interrupted at the time of the *onset* of the snap Craige and Fortuin claim that the sound is synchronous with the sudden halting of the opening excursion However the arrows pointing to the vibrations of the snap definitely point to the middle of the snap rather than its onset

If these published data of Craige and Fortuin are snaps they definitely occur prior to the completion of the opening movement by as much as 30 msec The claim that the onset of the snap is synchronous with the instant of fullest opening of the leaflets is contradicted by the published figures Their data appear to support the concept that the snap is a closing snap

Simon Rodbard, M.D
Director of Cardiology
City of Hope Medical Center
Duarte Calif 91010

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Smoking and cardiovascular disease

To the Editor

The article of Drs Hill and Wynder (AM HEART J 87 491 1974) brings out an interesting question regarding the possible different effects of high and low nicotine tobacco on coronary heart diseases (CHD) A similar suggestion was expressed by us several years ago[1] and was based on the data of our epidemiological studies among the farmers on the islands of Crete and Corfu, Greece for the past 15 years.

Although I am not sure how epidemiological studies can prove differences regarding CHD among smokers of low and high nicotine cigarettes when we are dealing with such a multifactorial catastrophic disease the truth is that morbidity and mortality rates from CHD among our populations are remarkably low These farmers smoke as heavily as other Western populations who have a high incidence of CHD but they smoke an oriental type of tobacco which contains less nicotine At the moment I do not know what is the significance of this observation but what at the same time is true is that these rural farmers are free from many other predisposing factors and present additional interesting characteristics regarding their life and diet which keep them probably relatively immune from this epidemic disease of our times

Professor Christ Aravanis M D
47 Queen Sophia Ave
Athens 140 Greece

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Reply

To the Editor

In the studies of Dr Avaranis and his associates (Avaranis, C Concordilas A Dontas A S Lekos, D and Keys A Circul XLI Suppl I 88 1970) of Greek men living on the islands of Crete and Corfu, smoking had no significant effect on the incidence of coronary heart disease (CHD) These authors considered serum cholesterol to be a risk factor for CHD while neither blood pressure nor physical exercise appeared to be related to the risk of CHD in these populations

As we noted in our paper smoking as a risk factor has its main impact on populations with a high rate of atherosclerosis Numerous studies have shown mortality rates of CHD in such populations to be higher in cigarette smokers than in non smokers The degree of atherosclerosis also increases directly with the number of cigarettes smoked and the number of years of smoking

It is evident therefore that smoking is an enhancing rather than an initiating factor in *CHD and affects primarily* populations with a high serum cholesterol level

Peter Hill, Ph.D
Ernest L. Wynder M D
Naylor Dana Institute for Disease Prevention
2 East End Ave
New York N Y 10021

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Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year

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cerned with many important physiologic regulatory phenomena in man and other animals Its relationship to hypertension and disease states is well known to most physicians physiologists and pharmacologists Nevertheless everyone interested in angiotensin will find this book extremely valuable for a review of the subject and as a reference The biologic production fate catabolism structure immunoassay, and bioassay are among the many aspects of the metabolism of angiotensin discussed. The role of angiotensin in primary and secondary hyperaldosteronism is also discussed extensively This is a highly recommended book about an *important bioregulatory agent The editors and contributors* have made an important addition to the medical literature

Books received

SURGICAL TREATMENT OF HYPERLIPIDEMIA By Henry Buchwald, M D Richard B Moore M D and Richard L. Varco M D New York 1974 American Heart Association Inc 37 pages Price $1 00

✓RECENT ADVANCES ON PAIN PATHOPHYSIOLOGY AND CLINICAL ASPECTS Edited by John J Bonica M D Paolo Procacci M D and Carlo A Pagni M D Springfield Ill Charles C Thomas Publisher 334 pages Price $19 75

MUSCLE BLOOD FLOW—ITS RELATION TO MUSCLE METABOLISM AND FUNCTION By O Hudlicka Dept of Physiology University of Birmingham Amsterdam 1974 Swets & Zeitlinger B V 152 pages

SCLERODERMA By Alfred J Barnett M D M R C P (Lond.) Specialist Physician and Associate Director of Clinical Research Unit Alfred Hospital Melbourne Australia Springfield Ill 1974 Charles C Thomas Publisher 220 pages Price $24 75

Announcements

Jane Nugent Cochems Competition

The University of Colorado School of Medicine announces the Twelfth Annual Cochems Competition A prize of $2 500 will be awarded to the author of the best paper concerning Thrombophlebitis and Basic Vascular Problems It should be concerned with the mechanisms or processes of vascular disease particularly thrombosis but not restricted to it Eligibility is limited to physicians subject to U.S income tax regulations Entries must be received in triplicate on or before November 30 1974 Inquiries regarding the competition and all manuscripts should be submitted to the Dean School of Medicine University of Colorado Medical Center 4200 East Ninth Ave Denver Colo 80220

Editorial

Surgery for aortic valve disease

James R. Galyean, M.D.
Akio Suzuki, M.D.
Thomas M. Blake, M.D.
Jackson, Miss.

Surgery for aortic valve disease is no longer a desperate effort to save a small number of patients with end stage heart disease. Patients symptomatic from aortic stenosis or regurgitation, even elderly ones, now may expect to have their lives not only prolonged by repair or replacement of the defective valve but also improved in a qualitative sense.

What evidence is there that these statements are true?

The natural history of patients with aortic valve disease has been well documented. When certain milestones are reached, notably angina pectoris, congestive heart failure, and, especially in those with aortic stenosis, syncope, the large majority must be expected to show a rapid decline in well being with death, frequently sudden, ensuing within a very few years.[1,2] Even with only minimal symptoms or none at all, prognosis is precarious when the hemodynamic burden is severe.[3,4] Medical treatment has done little to improve this outlook.

The operative and early postoperative mortality from aortic valve replacement has declined steadily from about twenty to thirty per cent ten years ago[2,5,6] to the present level of about five to ten per cent.[5,7,13] Operative mortality is related closely to the severity of the lesion at the time of surgery[14,15] and results can be expected to improve further when candidates can be identified earlier in the course of their disease before irreversible damage to the myocardium has occurred. Also, the results of surgery, not only immediate but long term as well, have become more gratifying; survival is no longer the criterion for success.

The predominant cause for late morbidity and mortality has been thromboembolism,[5,7,16,17] but in the past several years the incidence of this has been lessened by the use of valves of improved design with fewer thrombogenic properties,[5,10,12] and some no longer recommend routine anticoagulation in patients with aortic valve prosthesis. Anticoagulation itself may be a cause for morbidity or even mortality,[12] and the fact that thromboembolic complications of biologic valves (homografts) have been almost nil,[18] making the use of anticoagulants unnecessary, is one of the principle features that has recommended their use.

Dependability of the components of the prosthetic valves now in use has been improved to the point that dysfunction has been almost eliminated, and significant paraprosthetic regurgitation is now uncommon.[5,7,12] The prophylactic use of antibiotics has reduced the incidence of staphylococcal infections,[19] though infections, particularly with fungi and gram negative organisms, still occur and may necessitate removal of the prosthesis.[9,12,20] Low grade hemolysis is a problem in a small percentage of patients, but adequate hemoglobin levels can usually be maintained if urinary iron losses are replaced; hemolytic anemia of a degree to necessitate reoperation is rare.[5,11,12] Of patients operated upon recently, more than 80 per cent can expect to be not only alive five years after replacement of the valve but also reasonably active.[5,11,16,21,22] Our own experience confirms these observations with a perioperative mortality rate of eight per cent and a survival rate of 90 per cent at six years.

From the Departments of Medicine and Surgery, University of Mississippi School of Medicine, Jackson, Miss. 39216.
Reprint requests to: Dr. James R. Galyean, Department of Medicine, The University of Mississippi Medical Center, Jackson, Miss. 39216.
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The designation 'long term' applies to results in only a relative sense, of course few series having been followed more than 10 years after surgery What can be extrapolated from these 'long term," perhaps better described as "medium range," results in terms of present indications for aortic valve replacement?

The effect of a chronic pressure or volume load on the left ventricle is to induce certain anatomic and functional changes that tend to compensate for the mechanical disadvantage Thus ventricular dilation and hypertrophy may allow normal function of the ventricle as a pump, often for long periods but at the cost of deterioration of myocardial reserve,[23] and there is little evidence that such ultimately deleterious changes regress after the mechanical burden has been removed ventricular dysfunction still may be demonstrated, especially under the stress of exercise [24,25] Though this suggests that the indications for valve replacement should be defined by objective demonstration of ventricular dysfunction rather than by symptoms, it should be noted that the majority of patients are improved symptomatically, many returning to active and enjoyable lives [5,11,16,22] even though hemodynamic abnormalities persist

Despite intuitive recognition that the lot of patients with aortic valve disease would be better if valves were replaced before symptoms and irreversible changes have occurred, data to support such early intervention are not yet convincing, some mortality and morbidity inevitably attend any operative procedure Possible exceptions are those patients with specific high risk characteristics such as aortic stenosis with a large trans valvular gradient and progressive left ventricular enlargement, and those with severe aortic regurgitation [3,4]

In summary, valve replacement offers clear superiority over nonsurgical management in most patients with aortic valve disease who have developed symptoms Considering the gravity and prognosis of the disease the operative risk is acceptable and improving *Late morbidity* and mortality are significant but still represent amelioration of the natural history of the disease Although it is difficult at present to justify valve replacement in patients who are symptom free or have only little clinical evidence of limitation of cardiac reserve the trend is in that direction

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MP 202 microphone placed at the point of maximal cardiac impulse using a bandpass filter covering 40 to 200 Hz and recorded on a photographic Electronics for Medicine recorder Cardiac outputs were determined at rest after three minutes of 25 per cent MVC and after 30 seconds of 50 per cent MVC by the indicator dilution technique using indocyanine green dye and a Beckman cardiodensitometer

The stroke work index (SWI) of the left ventricle was calculated by the formula

$$\frac{SV \times (MLVS - LVEDP) \times 1\ 36}{100 \times BSA}$$

where SV = stroke volume in milliliters MLVS = mean left ventricular pressure during ejection determined by planimetric integration and expressed in millimeters of Hg LVEDP = left ventricular end diastolic pressure expressed in millimeters of Hg and BSA = body surface area in square meters

In this study an S_4 sound was considered to be present when a low pitched sound was recorded on the phonocardiogram between the beginning of the P wave and the onset of the QRS of a simultaneous electrocardiogram No distinction was made between the first and second component of the S_4

Student s paired t test and Mann Whitney U test were used to evaluate the results

Results

The patients were divided into three groups according to the presence or absence of an S_4 sound recorded on their resting phonocardiograms and whether an S_4 developed during isometric exercise

The sustained S_4 group consisted of nine patients who had an S_4 sound at rest which persisted during the isometric exercise

The developed S_4 group was comprised of six patients who had a normal resting phonocardiogram and developed an S_4 sound during the isometric exercise

The no S_4 group was comprised of six patients who were catheterized for diagnostic reasons, i e nonspecific chest pain functional murmurs or hemodynamically insignificant valvular heart disease These patients were all found to be free of significant valvular and myocardial disease and had normal left ventricular function S_4 was

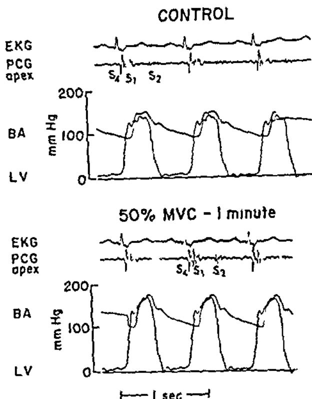


Fig 1 Sustained S_4 group Note the S_4 gallop in the resting phonocardiogram At 50 per cent MVC the S_4 remains the same while the left ventricular systolic pressure has increased from 140 to 180 mm Hg with a slight increase in left ventricular end diastolic pressure EKG = electrocardiogram PCG = phonocardiogram BA = brachial artery LV = left ventricle and MVC = maximum voluntary contraction

absent in all phonocardiograms at rest as well as during and after isometric stress

Phonocardiographic changes Two out of nine patients with a sustained S_4 at rest and during the isometric exercise showed an increase in amplitude of the S_4 during the isometric exercise (Fig 1) In the group of patients who developed an S_4 during handgrip (Fig 2) the S_4 was noted to appear between three and four minutes of 25 per cent MVC and as early as 30 seconds of 50 per cent MVC All but one persisted up to five minutes in the postexercise period The PR interval remained unchanged during the isometric exercise in patients in both groups No S_4 was present at rest during isometric stress or during the recovery period in the no S_4 group

Hemodynamic changes (Table I)

Peak left ventricular pressure All three groups

Clinical communications

Left ventricular function during isometric exercise (handgrip) significance of an atrial gallop (S_4)

Oscar A Matthews, M D *
C Gunnar Blomqvist, M D **
Lawrence S Cohen, M D ***
Charles B Mullins M D **
Dallas, Texas

In the absence of atrioventricular conduction disturbances, an atrial gallop fourth heart sound (S_4),† has been considered to be abnormal when audible in adults[1 2] It is present in a variety of clinical conditions and particularly common in systolic overload of the left ventricle,[1 3 4] in ischemic heart disease[1] and in cardiomyopathies[4 5] The mechanism clinical significance and prognosis are still controversial[1 4] and there are recent studies suggesting that an S_4 is present by phonocardiogram as well as by auscultation in a large proportion of middle aged and elderly subjects without cardiovascular disease[6]

Previous workers have correlated the presence of an S_4 with hemodynamic findings at rest[3 5] but the relationship between left ventricular function as determined from direct hemodynamic measurement, and the presence or development of an S_4 under stress has not been studied until recently[7] In the present investigation the left ventricle was challenged with an acute stress, predominantly a pressure load induced by a sustained isometric forearm contraction (handgrip),[8] and observations were made on the presence or development of an S_4 The use of isometric exercise for evaluation of left ventricular function is now a well established procedure[9-17]

Methods

Twenty one patients with various cardiac diagnoses (excluding A V blocks, atrial fibrillation, or hemodynamically significant regurgitant lesions) were studied during diagnostic cardiac catheterization

Right and left heart catheterizations including left ventricular cineangiograms were performed in all patients Coronary angiograms were completed in 16 of the patients Prior to the catheterization, the force developed during a maximal voluntary forearm contraction (MVC) was measured in each subject by utilizing a spring loaded hand dynamometer* The highest value obtained during three all out efforts was taken to represent MVC During left heart catheterization resting hemodynamic data were obtained. The patients immediately thereafter performed a steady handgrip for three to five minutes at 25 per cent MVC, again recording hemodynamic data After a recovery period of at least five minutes a 50 per cent MVC was performed for one to two minutes Simultaneous phonocardiogram, electrocardiogram, and left ventricular and brachial artery pressures were recorded continuously in the supine position The phonocardiogram was recorded with a Gulton

From the Pauline and Adolph Weinberger Laboratory for Cardiopulmonary Research of the Department of Internal Medicine University of Texas Southwestern Medical School at Dallas Dallas Texas

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Reprint requests Dr Charles B Mullins Cardiopulmonary-D 710 5323 Harry Hines Blvd Dallas Texas 75235

This work was completed during the tenure of Dr Matthews as a Postdoctoral Research Fellow supported by National Heart and Lung Institute Grant HL 05812 Dr Matthews present address is 1741 W Romneya Dr Suite B Anaheim Calif 92801

This work was completed during Dr Mullins tenure as a Teaching Scholar of the AHA and during Dr Blomqvist s tenure as an Established Investigator of the AHA

Dr Cohen s present address is Chief of Cardiology Yale New Haven School of Medicine 789 Howard Ave New Haven Conn 06510

†These terms will be used as synonymous and will refer to the sound that originates in the left ventricle during left atrial systole

*Stoelting Company Chicago Ill

MP 202 microphone placed at the point of maximal cardiac impulse using a bandpass filter covering 40 to 200 Hz and recorded on a photographic Electronics for Medicine recorder Cardiac outputs were determined at rest after three minutes of 25 per cent MVC and after 30 seconds of 50 per cent MVC by the indicator dilution technique using indocyanine green dye and a Beckman cardiodensitometer

The stroke work index (SWI) of the left ventricle was calculated by the formula

$$\frac{SV \times (MLVS - LVEDP) \times 1\,36}{100 \times BSA}$$

where SV = stroke volume in milliliters MLVS = mean left ventricular pressure during ejection determined by planimetric integration and expressed in millimeters of Hg *LVEDP* = left ventricular end diastolic pressure expressed in millimeters of Hg and BSA = body surface area in square meters

In this study an S_4 sound was considered to be present when a low pitched sound was recorded on the phonocardiogram between the beginning of the P wave and the onset of the QRS of a simultaneous electrocardiogram No distinction was made between the first and second component of the S_4

Student s paired t test and Mann Whitney U test were used to evaluate the results

Results

The patients were divided into three groups according to the presence or absence of an S_4 sound recorded on their resting phonocardiograms and whether an S_4 developed during isometric exercise

The sustained S_4 group consisted of nine patients who had an S_4 sound at rest which persisted during the isometric exercise

The developed S_4 group was comprised of six patients who had a normal resting phonocardiogram and developed an S_4 sound during the isometric exercise

The no S_4 group was comprised of six patients who were catheterized for diagnostic reasons, i e nonspecific chest pain functional murmurs or hemodynamically insignificant valvular heart disease These patients were all found to be free of significant valvular and myocardial disease and had normal left ventricular function S_4 was absent in all phonocardiograms at rest as well as during and after isometric stress

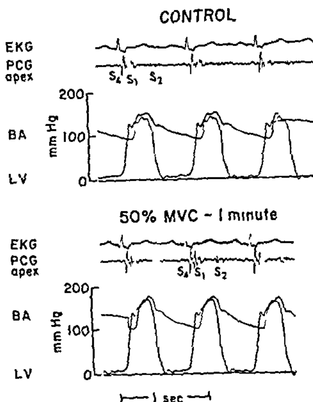


Fig 1 Sustained S_4 group Note the S_4 gallop in the resting phonocardiogram At 50 per cent MVC the S_4 remains the same while the left ventricular systolic pressure has increased from 140 to 180 mm Hg with a slight increase in left ventricular end diastolic pressure EKG = electrocardiogram PCG = phonocardiogram BA = brachial artery LV = left ventricle and MVC = maximum voluntary contraction

Phonocardiographic changes Two out of nine patients with a sustained S_4 at rest and during the isometric exercise showed an increase in amplitude of the S_4 during the isometric exercise (Fig 1) In the group of patients who developed an S_4 during handgrip (Fig 2) the S_4 was noted to appear between three and four minutes of 25 per cent MVC and as early as 30 seconds of 50 per cent MVC All but one persisted up to five minutes in the postexercise period The PR interval remained unchanged during the isometric exercise in patients in both groups No S_4 was present at rest during isometric stress, or during the recovery period in the no S_4 group

Hemodynamic changes (Table I)

Peak left ventricular pressure All three groups

Table I

Patient	Age	Sex	Diagnosis	Class	EF (%)	State	HR (beats/min.)	PLVP (mm. Hg)	LVEDP (mm. Hg)	SV (mL)	SWI (Gm. M/M²)
Group I—sustained S_4											
HR	48	M	CM	II	51	Control	63	95	12	62	32
						25%	74	125	18	57	36
						50%	76	160	18	58	43
WJ	50	F	CMA	II	85	Control	88	140	7	67	59
						25%	95	190	10	63	69
						50%	102	200	13	55	67
AB	41	F	CM	II	85	Control	70	130	9	87	70
						25%	80	150	10	90	86
						50%	88	195	10	76	94
CI	56	M	HBP	II	70	Control	76	180	14	77	79
						25%	75	190	17	77	85
						50%	80	204	18	76	89
LF	59	M	IHD	III	20	Control	76	128	20	54	36
						25%	97	175	54	41	32
						50%	87	160	43	39	31
LPK	46	M	IHD	III	42	Control	68	99	6	45	28
						25%	84	128	7	61	48
						50%	100	124	12	47	29
ID	50	M	IHD	II	50	Control	80	156	5	80	78
						25%	92	168	5	94	100
						50%	94	200	12	89	117
VI	50	F	VHD	II	50	Control	80	128	10	75	53
						25%	80	160	12	82	69
						50%	80	160	14	81	69
LC	27	F	CM	II	53	Control	63	130	11	71	57
						25%	89	172	13	63	66
						50%	112	196	20	53	65
Mean	47				56	Control	75	132	10	69	55
Mean						25%	85	162	16	70	66
p <							0 05	0 001	0 2	0 8	0 01
Mean						50%	91	178	18	64	67
p <							0 02	0 001	0 01	0 2	0 025

EF = ejection fraction HR = heart rate PLVP = peak left ventricular pressure LVEDP = left ventricular end-diastolic pressure SV = stroke volume *SWI = stroke work index Class = New York Heart Association functional classification control = rest, 25 per cent = 25 per cent maximum voluntary* contraction 50 per cent = 50 per cent maximum voluntary contraction CM = cardiomyopathy CMA = calcified mitral annulus HBP = systemic hypertension IHD = ischemic heart disease VHD = valvular heart disease and N = normal. P values refer to comparison of isometric period with control

Cineangiogram technically inadequate for measurement of EF

responded with a significant rise in peak left ventricular pressure from their control at both levels of isometric exercise All groups had an equivalent pressure change at 25 per cent MVC At 50 per cent MVC the no S_4 group had a 40 mm Hg mean pressure rise, the sustained S_4 group had a 46 mm Hg mean pressure rise, while the developed S_4 group only had a 17 mm Hg mean increase ($p < 0\ 05$)

Stroke volume The no S_4 group and the sustained S_4 group experienced no significant change in stroke volume at both levels of isometric exercise while the developed S_4 group showed a significant fall in mean stroke volume (9 5 ml) at 50 per cent MVC from the control ($p < 0\ 05$)

Heart rate All groups demonstrated a significant increase in heart rate from their control at both levels of isometric exercise There was no significant difference in heart rate changes between the groups at either level of isometrics

Table I—Cont'd

Patient	Age	Sex	Diagnosis	Class	EF (%)	State	HR (beats/min.)	PLVP (mm. Hg)	LVEDP (mm. Hg)	SV (mL)	SWI (Gm. M/M²)
Group II—developed S_4											
JS	34	M	CM	III	60	Control	88	120	5	51	42
						25%	94	130	10	50	43
						50%	108	140	17	44	39
JJ	26	M	CM	II	22	Control	86	150	10	55	55
						25%	90	165	14	67	71
						50%	108	180	28	47	52
MG	39	M	IHD	II	26	Control	75	140	25	69	55
						25%	104	185	38	49	44
						50%	109	180	50	51	42
JMcK	46	M	IHD	II	49	Control	85	120	12	79	52
						25%	95	142	18	68	52
						50%	104	140	22	60	42
FW	44	M	IHD	II		Control	73	110	14	80	43
						25%	81	175	26	69	56
						50%	84	140	28	85	54
NMcK	35	F	CM	III	47	Control	88	167	8	38	43
						25%	110	177	13	23	27
						50%	114	130	14	28	23
Mean	37				41	Control	82	135	12	62	48
Mean						25%	96	162	20	64	49
p <							0.025	0.05	0.01	0.20	0.9
Mean						50%	105	152	27	53	42
p <							0.001	0.20	0.005	0.05	0.3
Group III—no S_4											
LA	61	F	VHD	I	79	Control	76	138	4	78	59
						25%	90	195	9	76	83
						50%	100	220	15	69	84
RT	33	M	N	I	69	Control	54	110	10	108	71
						25%	70	150	18	94	76
						50%	78	160	20	103	85
MS	55	M	IHD	II	49	Control	87	127	8	55	39
						25%	95	155	10	57	49
						50%	100	170	14	56	52
GG	39	M	VHD	I	77	Control	69	152	12	68	66
						25%	74	160	12	72	75
						50%	72	168	13	82	88
JL	33	M	N	I	82	Control	100	112	3	51	34
						25%	104	122	5	48	41
						50%	110	130	5	49	45
WH	46	F	IHD	III	53	Control	72	130	12	85	63
						25%	76	140	14	84	70
						50%	78	158	15	82	74
Mean	45				68	Control	76	128	8	74	55
Mean						25%	85	154	11	72	66
p <							0.02	0.05	0.05	0.50	0.02
Mean						50%	90	168	14	74	71
p <							0.02	0.01	0.025	0.90	0.005

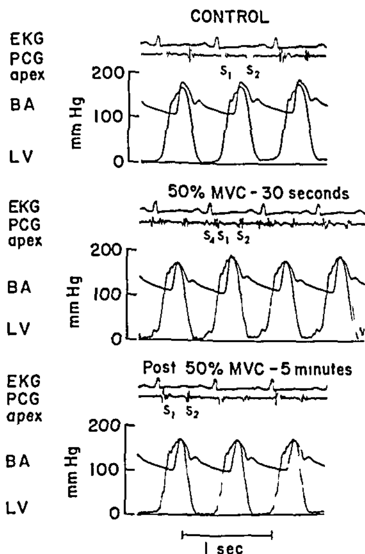


Fig 2 Developed S_4 group At 50 per cent MVC an S_4 gallop developed Mechanical alternans and a sizable atrial kick in the left ventricular pressure tracing occurred at 50 per cent MVC The phonocardiogram and the pressure tracings returned to the control state at five minutes postisometric exercise Abbreviations are the same as in Fig 1

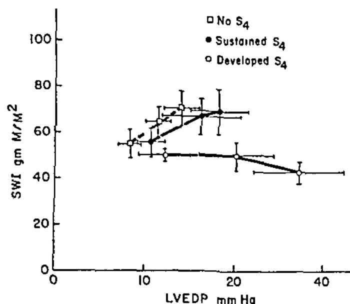


Fig 3 Illustrated are the mean left ventricular function curves for the three groups of patients Note the similarity between the curves from the no S_4 patients when compared with the patients with sustained S_4 The curve from the developed S_4 group is distinctly different and abnormal Standard errors are shown SWI = stroke work index and LVEDP = left ventricular end diastolic pressure

Systemic vascular resistance All three groups slightly increased their systemic vascular resistance at both levels of stress, however, these were not statistically significant increases at either exercise level when compared with resting values and the difference between the groups was not significant

Left ventricular end-diastolic pressure In the no S_4 group the left ventricular end diastolic pressure was normal at rest and increased only slightly with isometric exercise In the sustained S_4 group at rest the left ventricular end diastolic pressure was normal in seven patients slightly elevated in one patient (14 mm Hg), and definitely elevated in another patient (20 mm Hg) In the developed S_4 group at rest, four patients had normal left ventricular end diastolic pressure, slightly elevated in one patient (14 mm Hg) and definitely elevated in another patient (25 mm Hg) In both the sustained S_4 and the developed S_4 groups, the handgrip contraction resulted in significant elevations in left ventricular end diastolic pressure from the control values (Table I) However the developed S_4 group had a greater increase in left ventricular pressure than did the sustained S_4 group ($p < 0.10$)

Left ventricular function curves (Table I and Fig 3) Left ventricular function curves were constructed by relating stroke work index (SWI) in gram meters per square meter (Gm M/M²) to left ventricular end diastolic pressure (LVEDP) in millimeters of Hg [8,12] All patients in the no S_4 group developed an increase in stroke work index with small increases in left ventricular end diastolic pressure indicating a normal left ventricular response In the sustained S_4 group seven out of the nine patients demonstrated an increase in both SWI and LVEDP at 25 per cent and 50 per cent MVC also suggesting a normal response to the isometric contraction One patient (LF) had a clearly abnormal response characterized by large increments in LVEDP with a decrease in SWI One patient (LPK) had no change in SWI with increasing LVEDP

In the developed S_4 group five out of six pa

tients showed no change or a fall in SWI despite a significant elevation in LVEDP consistent with an abnormal left ventricular response to the handgrip test One patient (JJ) had a normal response to isometric exercise at 25 per cent MVC but at 50 per cent MVC demonstrated a drop in SWI to control level despite considerable elevation in LVEDP (indicating that left ventricular dysfunction developed at the higher work load)

The mean left ventricular function curves are illustrated in Fig 3 It is clear that the mean curves of both the no S_4 group and the sustained S_4 group closely parallel each other while the curve for the developed S_4 group is flat indicating a depressed left ventricular function

The slopes of the individual left ventricular function curves were measured in angular degrees for statistical analysis by the nonpaired Student t test No significant difference was found between the slopes of ventricular function curves in the no S_4 and the sustained S_4 groups however highly significant differences were present between the group that developed an S_4 and the other two groups i e no S_4 ($p < 0.001$) and sustained S_4 ($p < 0.01$)

Discussion

A number of reports have appeared correlating the S_4 gallop with basal hemodynamics [3,5] Shah and Yu[4] found the cardiac index and the left atrial mean pressure to be normal in patients with an S_4 and either myocardial disease or aortic stenosis Others[2] have stated that an S_4 gallop is frequently associated with an elevated left ventricular end diastolic pressure This contention is supported by the results of studies on S_4 gallops in subjects with left ventricular outflow tract obstruction [3,5] In patients with aortic stenosis the presence of an S_4 correlates with the severity of obstruction [5] On the other hand, Rectra and co workers[6] have recently presented data suggesting that an S_4 is present in a majority of ambulatory patients in the age range of 50 to 80 They considered the mere presence of an S_4 by phonocardiogram as well as by auscultation unrelated to cardiovascular status but pointed out that a loud S_4 implies advanced cardiac disease or hypertension It is apparent that there is a tenuous relationship between the presence of an S_4 and abnormal basal hemodynamics

The objective of this investigation was to assess the significance of the absence presence or development of an S_4 gallop during isometric exercise using left ventricular function curves obtained by direct hemodynamic measurements

Left ventricular function was assessed by relating stroke work index (SWI) with left ventricular end diastolic pressure (LVEDP) [8,12] The no S_4 group and the sustained S_4 group had a normal mean LVEDP and demonstrated an increase in both mean SWI and mean LVEDP at 25 per cent and 50 per cent MVC suggesting a normal left ventricular response to isometric stress (Fig 3) The developed S_4 group on the other hand had a higher but still normal mean LVEDP and demonstrated no significant change in SWI despite a marked increase in mean LVEDP at 25 per cent MVC and an actual fall in mean SWI with further increase in mean LVEDP at 50 per cent MVC indicating an abnormal left ventricular response to isometric stress (Fig 3) The use of the dye dilution method to measure cardiac output during exercise at the level of 50 per cent MVC may be criticized on the grounds that a true steady state did not exist However Fig 3 clearly demonstrates that the results at the 50 per cent level were directionally similar to the results obtained during steady state at the 25 per cent level and only served to amplify the trend already evident at the lower load

Siegel and co workers[19] performed noninvasive studies in a series of selected patients with clinical evidence of arteriosclerotic heart disease or myocardiopathy The majority of their 33 patients had an S_4 at rest but development of an S_4 during isometric exercise was noted in 6 out of 10 patients without S_4 at rest

Cohn and co workers[7] recently studied a series of 61 patients with chest pain and no S_4 on their resting phonocardiogram including 29 patients who had simultaneous phonocardiograms and hemodynamic studies Development of an S_4 was associated with significant angiographic abnormalities Fifty eight per cent of the patients with abnormal coronary angiograms developed an S_4 versus 15 per cent in the group with normal coronary arteries Only the group of patients who developed an S_4 demonstrated a significant increase in left ventricular end diastolic pressure during isometric exercise Simultaneous measurements of end diastolic volume (corrected for body surface) and end diastolic pressure at rest indicated that the volume pressure relationship also was

abnormal in the group that developed an S_4 suggesting decreased left ventricular compliance

The genesis of an S_4 gallop was recently discussed by Craig[2] using the left ventricular pressure volume relationship to explain the appearance of a fourth heart sound. He postulated that an S_4 occurs at a critical LVEDP which can be reached by a small inflow of blood either at a small end diastolic volume in the hypertrophied heart or by a larger end diastolic volume in a more compliant, dilated ventricle

The development of an S_4 gallop during isometric exercise is probably related to an increase in left ventricular volume during the increase in afterload with isometric exercise This is reflected by the increase in left ventricular end diastolic pressure during isometric contraction as peak left ventricular pressure increased. An acute increase in left ventricular size could result in enough resistance in atrial systole to produce an S_4 gallop

The possibility of an acute change in compliance (shift in the left ventricular pressure volume curve) explaining the change in LVEDP without a volume change in any given patient is unlikely since it has been shown that no significant change in left ventricular end diastolic distensibility occurs with moderate changes in heart rate[17-20] changes in sympathetic activity, or changes in vagal activity[21-23] Furthermore it has been shown that an increase in afterload will result in a larger end diastolic volume[24,25] Acute left ventricular ischemia during isometric exercise could have produced an acute change in compliance but no patient had angina or S T abnormalities suggesting acute myocardial ischemia during the procedure Thus it can be assumed that the increase in LVEDP observed during the isometric contraction also reflects an elevation in left ventricular end diastolic volume This volume increase may occur at a critical point on the pressure volume curve resulting in the development of an S_4

The data presented by Cohn and co workers[7] suggesting decreased left ventricular compliance in patients who developed an S_4 do not necessarily favor an acute compliance change as the major mechanism responsible for the development of an S_4 since their data were obtained at rest and presumably reflect a chronic change of the pressure volume relationships

We conclude from this investigation that the development of an S_4 with isometric stress usually indicates a significant abnormality of left ventricular function not appreciated with resting observations This simple isometric stress test, sustained handgrip, may be a useful bedside tool in evaluating left ventricular function in patients suspected of having heart disease

Summary

The clinical significance of an atrial (S_4) gallop remains controversial The present study was undertaken to investigate whether the development of an atrial gallop (S_4) during stress correlated more closely with an abnormal left ventricular function than the presence of an S_4 at rest. Left ventricular function was assessed by relating changes in SWI to left ventricular end diastolic pressure during isometric exercise at 25 per cent and 50 per cent of a maximum voluntary handgrip contraction A phonocardiogram was recorded continuously during the procedure

Six patients with no S_4 at rest or during isometric exercise all had normal ventricular function curves Six patients had no atrial gallop at rest but developed an S_4 during isometric exercise In this group all but one patient had an abnormal left ventricular function curve Finally, nine patients had an S_4 at rest as well as during isometric exercise Seven of these patients had a normal left ventricular function curve

The results suggest that the development of an atrial gallop during isometric stress may be a more reliable indicator of left ventricular dysfunction than the presence of an S_4 at rest Therefore isometric exercise can be employed as a bedside procedure for evaluation of left ventricular function

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The effects of carotid sinus pressure in re-entrant paroxysmal supraventricular tachycardia

Mark E Josephson M D
Stuart E Seides M D
William B Batsford, M D
Anthony R Caracta, M D
Anthony N Damato M D
John A Kastor M D
Staten Island N Y and Philadelphia, Pa.

The use of carotid sinus pressure (CSP) in the diagnosis and management of paroxysmal atrial tachycardia (PAT) has long been recognized It has been stated that abrupt termination of a supraventricular tachycardia is diagnostic of PAT while gradual slowing of the rhythm is most consistent with sinus tachycardia [1-5] In the present study we will report that the rate during re entrant of PAT usually slows prior to termination by CSP

Methods and Materials

Eighteen patients (Table I) with typical A V nodal re entrant PAT as defined by Bigger and Goldreyer,[6, 7] and Goldreyer and Damato[8] were studied Fifteen were evaluated using His bundle electrocardiography and the extrastimulus method [6 7 9 10] A tripolar electrode catheter was passed percutaneously through a femoral vein and positioned fluoroscopically across the tricuspid valve to obtain a His bundle electrogram An additional quadripolar electrode catheter was percutaneously passed to the high right atrium or coronary sinus, the proximal pair of electrodes recorded a local electrogram while the distal pair was used for pacing Using a specially built digital stimulator (Built by Murray Bloom Philadelphia Pa) which delivered impulses 2 msec in duration and at approximately twice diastolic threshold each patient was paced at a basic cycle length and progressively more premature impulses were introduced until enough A V nodal delay was produced to initiate PAT [8] Occasionally, multiple atrial stimuli were required to obtain the requisite A V nodal delay [8] Once stable PAT was established CSP was applied and the response recorded All data were stored on magnetic tape and later reproduced on photographic paper at a speed of 150 mm per second

In addition standard electrocardiograms (ECG s) were obtained in seven patients during PAT and response to CSP and/or the Valsalva maneuver was noted

Results

PAT was initiated by premature atrial depolarization in all patients In thirteen out of eighteen patients CSP terminated PAT In twelve of the thirteen patients atrial and ventricular rates gradually slowed prior to conversion to sinus rhythm In each of those patients in whom intracardiac recordings were made CSP produced a prolongation of A H interval prior to the termination of the tachycardia This response is demonstrated in Fig 1 The effect of the Valsalva maneuver on a spontaneous episode of PAT is similar (Fig 2) The Valsalva maneuver terminated tachycardia in one patient after a gradual slowing There were no untoward effects of CSP In one patient CSP terminated the PAT abruptly

From the Cardiopulmonary Laboratory United States Public Health Service Hospital Staten Island, N Y the Hospital of the University of Pennsylvania and the Cardiovascular Section Department of Medicine University of Pennsylvania School of Medicine Philadelphia Pa

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Reprint requests Dr Mark E Josephson Section of Cardiology Hospital of the University of Pennsylvania Philadelphia Pa 19104

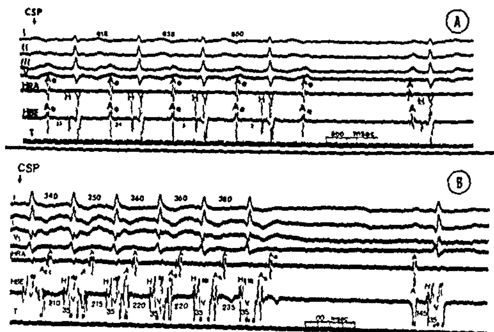


Fig 1 Effect of carotid sinus pressure on PAT Panels *A* and *B* are arranged from top to bottom as standard ECG Leads I II III, and V_1 a high right atrial electrogram (HRA) His bundle electrogram (HBE) and time lines (T) at 10 and 100 *msec A represents atrial echo beats H* represents His bundle depolarization, and V represents ventricular depolarization It is readily apparent that the R R intervals gradually prolong prior to the termination of the arrhythmia. This slowing occurs as A V nodal conduction time prolongs as measured by the A to H interval

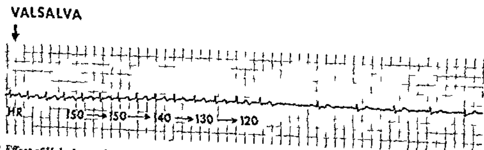


Fig 2 Effect of Valsalva on PAT This is a standard ECG Lead I from patient R W during a spontaneous episode of PAT The Valsalva maneuver gradually slowed the heart rate (HR) from 150 to 120 prior to termination of the arrhythmia.

Discussion

Goldreyer and colleagues[6,8] have established that the paroxysmal atrial tachycardia is usually due to re entry within the A V node These investigators have shown that the A V nodal re entry is dependent upon a critical amount of delay in A V nodal conduction resulting most commonly from an atrial premature beat Carotid sinus pressure and/or other vagal maneuvers are the first mode of therapy of this arrhythmia and are successful in perhaps 80 per cent of the cases[2] It has been accepted that conversion to normal sinus rhythm is abrupt and rarely is it accompanied by a gradual slowing of the rapid ventricular rate before resumption of a normal sinus rhythm[1,5] In contrast gradual slowing of a supraventricular tachycardia is thought to be characteristic of sinus tachycardia[1-5] We have seen thirteen cases of PAT broken with CSP—all but one of which showed slight slowing prior to termination It is most interesting that with the use of His bundle electrograms it could be demonstrated that CSP produced prolongation of the A H interval suggesting progressive A V nodal conduction delay prior to termination of the arrhythmia In addition we have demonstrated similar behavior in a patient during Valsalva maneuver (Fig 2) This response is not unex

Table I

	Patient	Age Sex	Cardiac diagnosis	Medications
1	R W	38 F	Normal	None
2	H H	65 M	ASHD s/p IMI	Quinidine 200 mg every 6 hours none for 24 hours
3	J P	58 M	Normal	Quinidine 200 mg every 6 hours none for 3 weeks
4	W B	55 M	ASHD	Procainamide 1 gm every 6 hours none for 24 hours
5	L D	35 F	Normal	None
6	M H	62 M	ASHD s/p IMI	Digoxin 0 25 mg daily
7	C A	20 M	None	None
8	M B	17 F	None	None
9	C K	38 F	None	Dilantin 400 mg daily
10	H C	21 M	?ASHD positive treadmill	None
11	G F	35 F	Lown Ganong Levine syndrome	None
12	K M	28 F	Lown Ganong Levine syndrome	None
13	R T	68 M	ASHD LBBB	None
14	I G	63 F	None	None
15	F M	57 M	ASHD	Digoxin 0 25 mg daily Procainamide 500 mg every 6 hours none for 24 hours
16	H W	29 M	None	None
17	J P	43 F	Mitral stenosis	Digoxin 0 375 Gm daily Lasix 80 Gm daily
18	E C	57 M	HCVD	Aldomet 500 every 6 hours

ASHD Atherosclerotic heart disease
IMI Inferior myocardial infarction
LBBB Left bundle branch block

pected when one considers the mechanism of the arrhythmia A V nodal re entry, which is the mechanism by which PAT is sustained, is critically dependent on the relationship of conduction and refractoriness of at least two functionally different pathways[8 11]

Thus vagal stimulation, which slows conduction and prolongs refractoriness within the A V node, would presumably slow conduction in the re entrant pathway prior to interrupting it[12 14] In our experience and in the experience of Goldreyer and Fisch (personal communication), this slowing prior to termination is the rule Thus, if during the management of an unknown supraventricular tachycardia CSP causes minimal slowing without termination this does not eliminate the possibility that the rhythm disturbance is PAT In such an instance one should repeat CSP after edrophonium phenylephrine, or digoxin for added vagal effect in an attempt to terminate the arrhythmia

Summary

The effect of carotid sinus pressure (CSP) on paroxysmal atrial tachycardia (PAT) was studied in eighteen patients In twelve of the thirteen patients in whom CSP terminated the arrhythmia gradual slowing occurred prior to conversion to sinus rhythm With the use of His bundle electrograms it could be demonstrated that this slowing was due to prolongation of conduction through the A V nodal re entrant pathway (increased A H interval) Thus slowing of a supraventricular tachycardia in response to CSP does not rule out the possibility that the arrhythmia is PAT Further vagal maneuvers may therefore, be indicated in the diagnosis and management of such an arrhythmia

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Day-to-day variation of the Frank electrocardiogram and vectorcardiogram in heart disease

P M Kini M D
P Ginefra, M D
H V Pipberger, M D
Washington D C

A number of reports on the variability of the electrocardiogram (ECG) in normal individuals have appeared in the literature [1-4] A detailed statistical analysis of daily variability of electrocardiographic measurements in the normal orthogonal ECG was reported by Willems Poblete and Pipberger [5] This analysis was based on data obtained from 20 normal subjects of both sexes and limits of variability were established and emphasized.

Studies on daily variation of electrocardiographic measurements in patients with heart disease are very few Simonson[6] studied the daily variability of ECG's of patients with coronary heart disease (CHD) and compared it with that found in a group of normal subjects Great variability especially in T wave amplitude was found in patients with CHD who had both normal and abnormal ECG's at rest Several investigations with long term monitoring in coronary care units or in ambulant patients have been done lately These have been concerned primarily with arrhythmias rather than daily variability of electrocardiographic measurements

The purpose of the present study was to observe the day to day variation of the orthogonal ECG and vectorcardiogram (VCG) in patients with hypertensive and/or CHD and to compare the results with those obtained on normal subjects by Willems Poblete and Pipberger [5] We hope the data presented will be of use to the clinician to decide whether changes observed in serial ECG s are indicative of an abnormality or are within the range of day to day variability Alterations in electrocardiographic patterns seen while monitoring patients in intensive care units may be interpreted as significant only when they exceed repeat variability ranges

Material and method

Patients for the study were selected from the antihypertensive and anti angina clinics of the Veterans Administration Hospital Washington D C The aim of selection was to find subjects whose clinical condition had remained stable for at least several weeks prior to the investigation Patients who had marked fluctuations in their blood pressure (BP) recent and frequent alterations in therapy cardiac failure significant electrolyte disturbances, drug toxicity renal failure or a recent change in the pattern of anginal pain were excluded from the study

Nineteen patients with sustained arterial hypertension and one patient with exertional angina formed the subjects of this investigation All were ambulatory males their ages ranged from 27 to 65 with a mean age of 49 ± 9 The patient with angina had had a documented myocardial infarction ten years ago Two of the patients with hypertension also had exertional angina and two others had diabetes mellitus controlled by diet alone

BP was recorded for each patient immediately before and after the ECG recordings A radiologic examination of the heart in postero an

From the Veterans Administration Research Center for Cardiovascular Data Processing Veterans Administration Hospital and the Departments of Medicine and Clinical Engineering The George Washington University Medical Center Washington D C

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Reprint requests Dr Hubert V Pipberger Veterans Administration Hospital 50 Irving St. N W Washington D C 20422

terior and lateral views was performed on all of the patients on one occasion during the ten day period.

During the period of study two patients were admitted to the hospital one with congestive heart failure and the other with chest pain suggestive of angina The latter patient was subjected to coronary arteriography which showed no evidence of significant coronary artery disease Daily ECG recordings were continued on both patients while they were in the hospital

Four of the patients with hypertension were using digitalis prior to and during the study in daily maintenance doses No patient had clinical evidence of digitalis toxicity during the period of observation One patient who was not on digitalis had frequent asymptomatic periods of ventricular bigeminy

Corrected orthogonal ECG s using the Frank lead system were recorded on magnetic tape on ten occasions on each patient during two consecutive five day periods separated by a two day weekend Records were taken with the patient in the recumbent position with the fourth intercostal space being used for placement of the chest leads Electrode locations on the chest were not marked in order to simulate the routine practice of electrocardiography The same technician operated the same recording equipment during the entire period of the study with a standard method of calibration No technical problem was encountered during the investigation.

Of the 200 ECG s recorded five tracings were excluded from the study because of recording errors The remaining 195 records were used for analysis Recording technique equipment characteristics and computer methods used for analysis of the ECG s have been detailed previously [7]

Fifty four measurements were computed on each of the records in order to observe day to day variation and the results were compared with observations made on normal individuals by Willems Poblete and Pipberger [5] The measurements were

(1) *Time measurements* P and QRS duration heart rate PR interval duration of Q R and S waves and the time from the beginning of QRS to the peak of the R wave (R peak time) in the three orthogonal leads

(2) *Amplitude measurements* Peak amplitudes of individual Q R S and T wave deflections in each of the orthogonal leads and magnitudes of spatial maximal QRS and T vectors and of maximal QRS and T vectors in the frontal (XY) sagittal (YZ) and transverse (XZ) planes

(3) *Angular measurements.* Directions of maximal QRS and T vectors in the three VCG planes and azimuth and elevation angles of spatial maximal QRS and T vectors

(4) *Amplitude ratios* Between Q and R waves (Q/R ratios) and between R and S (R/S ratios) in X, Y and Z leads

These measurements were obtained by computer for all beats available in six seconds of time covering at least one respiratory cycle [8]

The following method was used to determine day to day variability for each measurement (1) Calculation of each day s mean value—m_1 m_2 m_{10}—for each subject using all beats in a six second recording This allowed us to eliminate beat to beat variability[8 9] and respiratory variations

(2) Calculation of averaged mean from ten daily means for each subject

$$m_{AV} = \frac{m_1 + m_2 + \quad m_{10}}{10}$$

(3) Calculation of deviation d of each daily mean from m_{AV} for each subject

$$d_1 = m_1 - m_{AV} \quad d_2 = m_2 - m_{AV} \qquad d_{10} = m_{10} - m_{AV}$$

(4) The d values of all subjects were pooled together Mean standard deviation and 96 percentile range were calculated for the pooled data The 96 percentile range was used because the d values were not normally distributed. The upper limit of this range was used to express the extremes of day to day variability

Table I Day to day variation of time measurements

Measurement	Normal* (variation in msec.)		Cardiovascular disease (variation in msec)	
	Mean	96%	Mean	96%
P	6	26	4	23
P R interval	6	22	7	33
QRS	2	8	2	12
QX	1	4	1	4
QY	1	4	2	10
QZ	2	13	2	6

Measurements for normal in this Table are based on data of Will ms, Pobl te and Pipberger [5]

Table II Day to day variation of QRS and T amplitude measurements

Measurement	Normal* (variation in mV)		Cardiovascular disease (variation in mV)	
	Mean	96%	Mean	96%
QRS				
R in Lead X	0 14	0 61	0 09	0 36
R in Lead Y	0 06	0 23	0 06	0 25
R in Lead Z	0 09	0 35	0 08	0 45
QRS spatial maximum	0 11	0 50	0 10	0 35
Q in Lead X	0 01	0 04	0 01	0 04
Q in Lead Y	0 01	0 04	0 02	0 07
Q in Lead Z	0 04	0 13	0 03	0 16
T				
T in Lead X	0 04	0 13	0 05	0 17
T in Lead Y	0 03	0 11	0 03	0 12
T in Lead Z	0 03	0 09	0 03	0 16
T spatial maximum	0 04	0 14	0 04	0 15

Measurements for normal in this Table are based on data of Willems, Poblete and Pipberger [5]

Table III Day to day variation of angular measurements

Measurement	Normal* (variation in degrees)		Cardiovascular disease (variation in degrees)	
	Mean	96%	Mean	96%
Maximum QRS in XY plane	5	23	3	19
Maximum QRS in XZ plane	9	63	7	61
Maximum QRS in YZ plane	10	57	6	42
Azimuth QRS spatial maximum	7	32	7	58
Azimuth T spatial maximum	9	43	11	69

Measurements for normal in this Table are based on data of Willems Poblete and Pipberger [5]

Results

Results of day to day variability of the different parameters observed in this study and those found in normal subjects[5] are listed together for comparison in Tables I through III

Day to day variability of time measurements Daily variability of selected time parameters is listed in Table I Mean variations of all time measurements computed were almost identical for patients with heart disease and normal subjects The maximum variation for the P R interval and the Q duration in Lead Y was higher in heart disease The mean variation of R wave duration was 3 8 msec compared to 3 2 msec in the normal subjects the upper limit of 96 percentile range was 25 msec in heart disease as against 15 msec in normal subjects

Day to day variation of amplitude measurements Table II shows measurements of daily variation of amplitudes of selected QRS and T scalar and vector parameters Mean variability of these measurements was almost identical for subjects in the present study and for normal subjects The upper limit of 96 percentile range of variability for the QRS spatial maximum was lower in patients with heart disease than in normal subjects, variation of magnitude of maximal QRS vectors in the frontal and sagittal planes was correspondingly lower in patients with heart disease

Variation of angular measurements Mean and maximum variation of angular measurements are listed in Table III As in normal subjects variations in the frontal plane QRS angles were smaller than in the sagittal and transverse planes The maximum for the mean frontal plane QRS angle was 19° on either side of the mean giving a total variation of 38° compared to 46° in normal subjects

Amplitude ratios The maximal (96 per cent) change in Q/R ratio in Leads X, Y, and Z was 0 03 0 31, and 0 18 respectively and in the normal subjects 0 03, 0 05 and 0 76 The variation of Q/Ry ratio appears to be greater in heart disease but this ratio was obtainable only in 42 records which had a Q in Lead Y The Q/R ratio in Lead Z was less variable in heart disease than in the normal subject

Marked changes in the ECG were observed in two patients with hypertension during the period of study One patient a 61 year old male was admitted to the hospital on the second day of the study with dyspnea Clinical examination showed evidence of congestive heart failure Representative scalar leads and vector loops recorded during the ten day period are illustrated in Figs 1 and 2

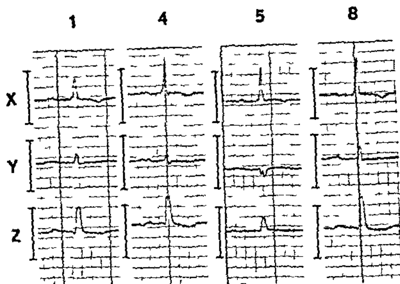


Fig 1 Serial ECG s recorded in a 61 year-old patient with hypertension. Note the development of a notched QS complex in Lead Y with disappearance of Q in Lead Z on Day 5 On Day 8 the record has reverted to the pattern of Day 1 The numbers on top refer to the day of recording. Vertical bars represent 2 mV calibration

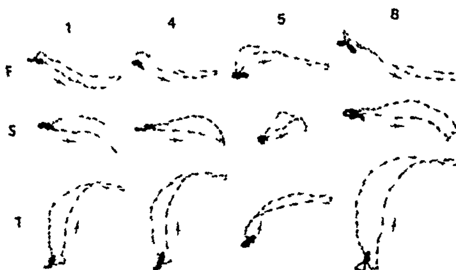


Fig 2. Vector loops (retouched) of the patient whose scalar leads are depicted in Fig 1 Note the superior shift of the frontal plane QRS axis on Day 5 There is also a loss of initial anterior forces in the transverse (T) plane The loops on Day 8 show a reversal of the patterns to that of Day 1

The ECG and VCG were consistent with left ventricular hypertrophy on Day 1 On Day 4 the frontal plane axis had shifted somewhat superiorly ECG on Day 5 showed a notched QS pattern in Lead Y and absence of Q in Lead Z The corresponding VCG showed superior orientation and clockwise rotation of the initial 25 msec. QRS forces consistent with an inferior myocardial infarction as well as some further superior shift of the frontal plane QRS axis The initial anterior forces in the transverse plane were diminished in comparison with the control tracings ECG and VCG on Day 8 showed a reversal of the patterns to that of Day 1 The patient had no chest pain during the entire period of observation Serial enzyme determinations showed no significant alterations

The second patient a 49 year old male was asymptomatic throughout the study ECG on Day 1 (Fig 3) showed RS pattern in Lead Y and no Q

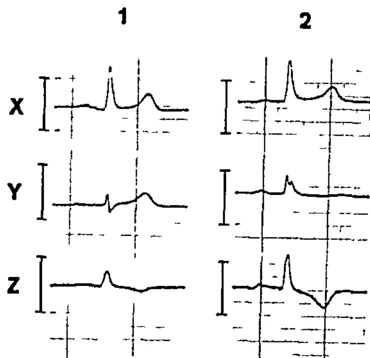


Fig 3 Scalar leads recorded ın a 49 year old patıent wıth hypertensıon Note that on Day 2 there was notchıng of the R wave ın Lead Y wıth dısappearance of the prevıously recorded S wave Lead Z shows a small notched Q wave whıch was not present on Day 1 The subsequent eıght recordıngs whıch are not presented ın the figure resembled tracıng 2

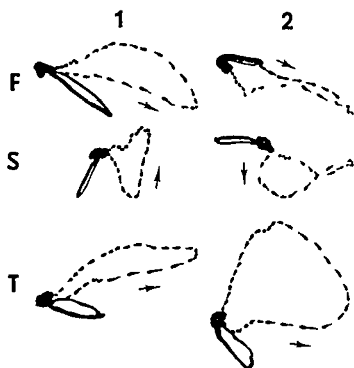


Fig 4 Vector loops of patıent whose scalar recordıngs are shown ın Fıg 3 Note that the frontal plane QRS rotatıon whıch was counterclockwıse on Day 1 has changed to a figure of eıght configuratıon on Day 2

ın Lead Z On Day 2 the S ın Lead Y had dısappeared and Lead Z now showed a small, notched Q wave The QRS duratıon also ıncreased from 100 msec on Day 1 to 115 msec on Day 2 Subsequent ECG s showed persıstence of the pattern of the second day untıl the end of the study Corresponding VCG s are shown ın Fıg 4 The frontal plane QRS rotatıon whıch was counter clockwıse on Day 1 changed to a figure of eıght on Day 2

All calculatıons were repeated on 18 patıents after excludıng the two patıents wıth sıgnıficant ECG changes from the group wıth a vıew to determıne whether these cases had ınfluenced the mean results Dıfferences were found for the followıng measurements maxımum daıly varıatıon of the amplıtudes of R and S waves ın Lead Y and the R wave ın Lead Z were 0 06, 0 07, and 0 07 mV respectıvely less than that observed for the entıre group of 20 patıents The upper lımıt of the 96 per cent varıatıon of the maxımal QRS vector ın the sagıttal plane was 0 28 mV ın the 18 patıents as agaınst 0 43 mV for the entıre group Mean varıabılıty of T amplıtude ın Lead Z also dımınıshed by 0 05 mV when the two patıents were excluded Maxımum and mean day to day varıatıon of other parameters showed no changes by exclusıon of the two cases

Dıscussıon

Our study demonstrates that consıderable day to day varıatıon of several electrocardıographıc parameters occurs ın patıents wıth heart dısease A majorıty of the patıents studıed had hypertensıon wıth or wıthout cardıomegaly Although only one patıent wıth overt coronary artery dısease (CAD) was ıncluded, two other patıents had clınıcal evıdence of CAD as well as hypertensıon It may also be assumed that a sıgnıficant percentage of the patıents wıth hypertensıon had CAD of varyıng degrees of severıty The results of our study therefore would be applıcable for patıents wıth hypertensıon and/or CAD

Day to day varıatıon ın tıme measurements, as ın normal subjects was relatıvely small The duratıon of the P wave and the QRS complex was remarkably stable Thıs may partly be explaıned by the consıstency of computer determınatıon of the begınnıng and end of ECG waves [9]

Varıatıons of many of the QRS amplıtude measurements ın patıents wıth heart dısease were sımılar to those observed ın normal subjects The upper lımıt of 96 percentıle range for varıatıon of R amplıtude ın Lead Z and the maxımal QRS vector ın the sagıttal plane was hıgher ın the heart dısease group than ın normal subjects but the mean was sımılar ın both groups of

subjects Variability of R amplitude in Lead X was surprisingly lower in patients with heart disease than in subjects with no heart disease

Variability of T wave measurements observed in this study was similar to that found by Willems Poblete and Pipberger[5] in normal subjects As the T wave amplitude and morphology are influenced by a variety of factors marked lability of the T wave was anticipated In patients with heart disease factors which are not applicable to normal subjects like ischemia drugs and electrolyte disturbances cause significant alterations in the T wave It was therefore surprising to note that the magnitude of T variability did not differ markedly from that in normal subjects More variability of T wave probably would have been observed if the study was not limited to patients in a stable clinical status

Day to day variation that occurred in our patients was not related to any change in symptoms or significant alterations in clinical findings Beat to beat variation and variations as a result of respiration were eliminated by a process of averaging complexes recorded in a period of six seconds As the electrode positions were unmarked to simulate normal recording conditions inadvertent changes in electrode position play an important role in the variability observed from day to day The effects of displacement of electrodes on amplitudes recorded by the orthogonal lead systems have been reported previously[10, 11] Furthermore Willems Poblete and Pipberger[5] demonstrated that marking of location of the chest electrodes reduces variability of amplitude and angular measurements This procedure however is not practical for routine clinical ECG recording

Two of the 20 patients had abrupt and marked alterations in their ECG pattern during the study In one patient changes in Lead Y and the frontal and sagittal plane loops suggested loss of inferior wall forces However rapid return to the original pattern and absence of enzyme changes did not favor a diagnosis of myocardial infarction The transitory electrocardiographic changes probably are due to electrophysiologic inertness of the myocardium similar to that occurring in myocardial infarction De Pasquale Burch and Phillips[12] have proposed that transitory Q waves occurring in the absence of myocardial infarction may reflect a temporary loss of action potential due to localized alteration in the cell membrane rather than cell death Although electrically inactive the cell may be viable and hence regain electrical activity with consequent disappearance of the Q wave

Transitory abnormal Q waves have also been described in the absence of coronary artery disease in conditions like subarachnoid hemorrhage[13] pancreatitis[14] hyperkalemia[15] and shock and severe metabolic stress[16] Our patient had no clinical or laboratory evidence of any of these conditions

Sudden QRS axis shifts observed in sequential ECG s may also be the consequence of block in the division(s) of the left bundle branch Numerous reports of such shifts due to left anterior hemiblock (LAHB) and left posterior hemiblock (LPHB) have appeared in the literature Cohen and co workers[17] and Fernandez Scebat and Lenegre[18] were able to produce transitory patterns of hemiblock in man The average QRS rotation was only 34 in LAHB and 28 in LPHB However it is conceivable that much larger shifts may occur in the presence of disease involving one or more divisions of the left bundle to varying and often unequal degrees The QRS axis shifts that occurred in our patients probably reflect alterations in conduction Prolongation of the QRS duration from 100 msec to 115 msec in one of the patients also favors the diagnosis of aberrant conduction.

On the basis of the present study it may be concluded that the magnitude of day to day variability of the ECG in patients with clinically stable heart disease is not significantly different from that in normal subjects However electrocardiographic changes due to alterations in conduction seem to be common in patients with heart disease

Summary

Day to day variation of the Frank electrocardiogram and vectorcardiogram was studied in 20 patients with clinically stable hypertensive and/or coronary heart disease Ten recordings were made on each patient during two consecutive five day periods separated by a two day weekend. Fifty four selected measurements including durations amplitudes amplitude ratios spatial magnitudes and angles were computed on each of the records Mean and maximal day to day variations of these measurements were compared with variations observed in 20 normal subjects reported in a previous study

Although considerable repeat variability was

observed for several parameters, the magnitude of variability was not significantly different from that in normal subjects However, abrupt and marked change in the electrocardiographic pattern seen in two patients suggests that sudden alterations in conduction may be common in patients with heart disease

The data presented can be helpful in assessing the significance of variations observed in serial electrocardiography in clinical practice

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A pilot study of streptokinase therapy in acute myocardial infarction observations on complications and relation to trial design*

Editorial Committee
Paul M Ness, M D
Toby L Simon M D
Christine Cole
Abe Walston M D
Bethesda, Md

The use of streptokinase (SK) in acute myocardial infarction has been a subject of intense medical interest following the demonstration that this agent can dissolve human thrombi The first trial of SK in myocardial infarction was reported by Fletcher and colleagues in 1959[1] This initial use of SK was followed by twenty one feasibility studies of fibrinolytic agents (most with SK but also with urokinase or plasmin) Encouraging results from these feasibility studies led to the undertaking of ten large scale cooperative clinical trials[2-11] Early trials of SK in acute myocardial infarction demonstrated a significant mortality reduction in patients treated on general medical wards Later trials attempting to show clinical efficacy in coronary care unit patients have been unsuccessful in demonstrating a statistically significant mortality reduction[12]

Cardiovascular disease is the number one cause of death in the United States A therapy offering the possibility of a 25 per cent reduction in mortality in patients hospitalized with acute myocardial infarction could salvage as many as 80 000 lives per year[13] These considerations prompted the National Heart and Lung Institute to organize a trial of SK in acute myocardial infarction To demonstrate a reduction in mortality of 25 per cent with SK assuming that the 21 day mortality from acute myocardial infarction is 15 per cent in control patients a minimum sample size estimate was calculated to be approximately 2 000 patients in each treatment group A protocol was written to test the hypothesis that an infusion of SK will decrease the mortality from acute myocardial infarction The protocol was designed to provide a controlled randomized modified double blind mortality study which was named Streptokinase Myocardial Infarction Trial (SMIT) To test the workability of the protocol and the feasibility of the large scale clinical trial a group of eight institutions was selected to perform a pilot study

The pilot study was not expected to be part of a definitive trial It was understood that no statistical significance could be attached to the mortality findings of the pilot study because of the small number of patients We have however

From the National Heart and Lung Institute Bethesda

This coope ativ pilot study was suppo ted and coo dinated by the Na ti nal Heart and Lung Institute (NHLI)

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*By mutual agreement f all participants, official publ cations f om this trial will be prepared by an editorial committe and submitted by all particip nts. *Principal in estigat s* Dr Dani l C Allensw rth (Un vers ty of T xas G l eston) Dr Edward Genton (University of Colorado Medical Cent Den er) D Georg A K lser (Georg Wa h ngton Univers ty M dical Cente Wash ngton D C) Dr Joseph V Messer (Boston C ty Hosp tal, Boston) Dr Richa d D S ut ter (Marshfi ld Clinic Foundation) Dr Abe W lston (Durham Veterans Administration Hosp tal) Dr Howard Warn and Dr James F Spann, Jr (T mple Univers ty School of Medic ne Philadelphia) and Dr Park W Willis, III (Univ rs ty of M chigan M dical Center Ann A bor) *NHLI medical and tatistical coo dination* Chri t ne Cole Dr C. Steph n Foster Dr P ul M. Ness Dr Toby L. S mon nd Dr James M. Stengle *Policy board* D Sol Sherry (Temple Uni sity Philadelphia) Jerome Cornfield (G rge Wash gton Un er ty Washington, D C.) Dr Richa d V Ebert (Uni ers ty of Minnesota, M nn apolis) and Dr James M Stengle (Nati nal Heart nd Lung Institute Washington, D C.)

chosen to present our data on the incidence of complications of SK therapy in a group of myocardial infarction patients carefully studied by a collaborative group of cardiologists working in representative coronary care units as useful general information

Methods

Patient accession began on Oct 22 1971, and 107 patients were entered into the pilot study before it was concluded on Nov 4 1972 The patients were randomized between two therapies, SK or control The initial control patients received heparin, and later control patients received glucose Two preparations of SK (Hoechst and Kabi) used during the pilot study were allocated by random techniques Every effort was made to insure the comparability of general care in the SK treated and control groups without imposing unnecessarily rigid restrictions or demands on the investigator The investigators were free to treat arrhythmias and congestive heart failure with their standard practices

Upon completion of the required diagnostic studies the patient's eligibility for inclusion into the trial was determined Patients who did not have either electrocardiographic or enzyme evidence of infarction within 24 hours of the onset of symptoms were excluded Informed consent was obtained from all patients included Random allocation into treatment groups was accomplished by the use of a series of sealed envelopes A therapeutic infusion was begun within one hour of treatment assignment The modified double blind study required that neither the patient nor physicians caring for the patient were informed of the treatment assignment Another physician was responsible for the therapeutic infusion A polyethylene catheter or scalp vein needle was positioned in a peripheral vein to permit continuous infusion During the time of therapeutic infusion, cutdowns, subclavian vein cannulations, femoral vein punctures and arterial invasive procedures were to be avoided

Knowledge of the results of a complete blood count including platelet estimation standard 12 lead electrocardiogram, Lee White clotting time or partial thromboplastin time chest radiograph and blood urea nitrogen or creatinine were required prior to eligibility determination A urinalysis, stool guaiac, cardiac enzymes ASO titer and thrombin time were also required baseline studies The existence of conditions contraindicating thrombolytic therapy excluded a number of patients The following list of conditions required exclusion of the patient from the trial major surgery within one month of therapy, minor surgical procedures within 10 days of therapy, cardiopulmonary resuscitation within 10 days of therapy, arterial punctures within 24 hours of infusion, cerebrovascular accident within one month of therapy an actively bleeding lesion, a congenital or acquired hypocoagulable state severe renal or hepatic insufficiency, treatment with SK or a streptococcal infection during the previous month active rheumatoid arthritis, rheumatic fever, tuberculosis, bacterial endocarditis, pregnancy or the first 10 days of the postpartum period, severe hypertension, and suspicion of an arterial aneurysm

All therapeutic infusions were administered by constant infusion pump Two hundred fifty thousand units of SK in 50 ml of 5 per cent glucose was administered intravenously in 20 minutes followed by a maintenance dose of 100,000 units per hour for twenty four hours One million two hundred thousand units of SK were dissolved in 50 ml of 5 per cent glucose which was given over 12 hours and then repeated In the case of control patients 50 ml of 5 per cent glucose was administered intravenously over 20 minutes followed by an additional 50 ml of 5 per cent glucose over 12 hours given twice The earlier control patients received a loading dose of 75 units per pound of body weight of aqueous heparin administered intravenously over 20 minutes followed by a maintenance dose of 10 units per pound per hour by a constant infusion pump Heparin was given as a loading dose and twelve hour infusions in 5 per cent glucose in an identical manner All dosages and procedures were selected to correlate with a planned simultaneous European multi institutional trial

Early termination of therapy was permissible if signs of toxicity or adverse reactions occurred. It was required that therapy be discontinued if (1) closed chest massage was performed (2) significant hemorrhage occurred (3) surgery became necessary (4) the patient suffered a cerebrovascular accident or (5) other serious adverse reactions thought to be secondary to the therapy occurred which were considered uncontrollable

Table I Patient characteristics by treatment group

	Streptokinase		*Control*	
	No	%	*No.*	%
Age				
‹40 years	7	13 2	2	3 7
40 49	10	18 9	15	27 8
50 59	14	26 3	19	35 2
60 69	15	28.3	13	24 1
70 75	7	13.2	5	9 3
Total	53	—	54	—
Average age	54 9 ± 11 8		55 3 ± 9 8	
Sex				
Male	43	81 1	45	83 3
Female	10	18 9	9	16 7
Past history				
Undocumented MI	6	11 3	3	5 6
Documented MI	11	20 8	15	27.8
Angina	27	50 9	33	61 1
CVA or TIA	1	1.9	4	7 4
Claudication or other peripheral arterial disease	6	11 3	3	5 6
Congestive heart failure	11	20 8	4	7 4
Systemic hypertension	12	22 6	15	27 8
Diabetes	10	18 9	5	9.3
Cigarette smoking	36	67 9	27	50 0
Drug therapy (within 2 months prior to admission)				
Anticoagulants	0	0 0	2	3 7
Cardiac glycosides	14	26 3	8	14 8
Diuretics	9	17 0	12	22 2
Antihypertensives	1	1 9	7	13 0
Antiangina drugs	11	20 8	12	22 2
Antiarrhythmics	3	5 7	2	3 7

Treatment regimens for anaphylactoid reactions hemorrhage and fever were standardized.

Results

A Patient characteristics and results of randomization During the pilot study 107 patients were studied at seven centers Fifty three received SK (Kabi, 25 Hoechst 28) and 54 received a control infusion The control group had eight patients receiving heparin, and 46 patients receiving 5 per cent glucose alone Table I shows the distribution of patients according to various characteristics upon entry into the study For most of the characteristics balance between treatment groups was reasonably good, particularly in view of the small sample under study More patients below the age or 40 and above the age of 60 received SK as compared to the control group The same proportion of males to females received each treatment. More control patients had a past history of documented myocardial infarction angina cerebrovascular disease and systemic hypertension a greater number of the SK treated group had a past history of peripheral arterial disease congestive heart failure diabetes and cigarette smoking More control patients received diuretics and antihypertensive therapy during the two months prior to admission The SK treated group had a larger number of patients who had been treated with cardiac glycosides during the two months before the current hospitalization

To gain a better appreciation of the differences between the control group and SK treated group the patients were evaluated by a retrospective construction of a modified Peel index developed at the University of Colorado [14] Pre infusion data were used whenever available infusion period data were considered if sufficient pre infusion in

Table II Distribution of modified Peel scores for 107 patients entered in the SMIT pilot study

Modified Peel score	SK	%	Control	%
0 4	13	(24 5)	9	(16 7)
5 8	15	(28 3)	24	(44 4)
9 12	13	(24 5)	16	(29 6)
13 16	10	(18 9)	2	(3 7)
17 19	2	(3 8)	1	(1 8)
> 20	0	(0 0)	2	(3 7)
Average	8 26 ±	4 52	7 98 ±	3 98

Table III Number of patients having hemorrhagic complications during and after infusion

Complication	SK	Control
Puncture site	22 (41 5)	4 (7 4)
Genitourinary	6 (11 3)	0 (0 0)
Gastrointestinal	8 (15 1)	3 (5 6)
Spontaneous hematoma	5 (9 4)	0 (0 0)
Intracranial	1 (1 9)	0 (0 0)
Other	6 (11 3)	3 (5 6)
Any hemorrhage—total	31 (58 5)	8 (14 8)
Fall in hematocrit > 5 pts	14 (26 4)	12 (22 2)

formation was not available Table II contains a summary of modified Peel scores for 107 patients entered in the SMIT pilot study The average Peel score for the SK group was 8 26 ± 4 52 as compared with the average Peel score of 7 98 ± 3 98 in the control group This difference was not statistically significant The patients at high risk (modified Peel scores greater than 13) were predominantly in the SK group

A total of 1 684 patients was screened at the eight centers for the possibility of being admitted to the study Of these 1 684 patients screened to obtain our series of 107 patients, 556 patients who subsequently evolved definite myocardial infarctions were excluded for the following reasons 196 had symptoms for greater than 24 hours before diagnosis 155 had a condition contraindicating thrombolytic therapy, 80 patients were over the age limit of 75 years, 69 patients lacked the private physician s consent and 23 patients refused to give individual informed consent The percentage of patients accessed into the SMIT pilot study was 16 1 per cent of all patients treated at the eight institutions for a documented myocardial infarction

B Complications of therapy Complications with therapeutic use of SK have been of two types those related to its principal mode of action, and those due to its antigenicity Hemorrhagic complications may occur fever, hypotension, and urticaria have also been reported Many of the pyrogenic and antigenic reactions may be due to impurities in the SK preparation Other reactions may be accounted for by inherent properties of the SK molecule itself and the patient's sensitivity through previous exposure to the streptococcus

The SMIT pilot study was designed to minimize hemorrhagic complications No invasive procedures were permitted for the first three days after the onset of therapy unless they were deemed crucial for optimal patient management. This prohibition was intended to reduce the high rate of hemorrhagic complications seen in the Urokinase Pulmonary Embolism Trial (UPET)[15] also sponsored by the National Heart and Lung Institute In that study, 45 per cent of the patients developed bleeding complications during the two week period of hospitalization It should be noted that the UPET protocol required extensive use of invasive procedures such as surgical cutdowns

The SMIT pilot study demonstrated bleeding complications in 31 or 58 5 per cent of patients receiving SK as shown in Table III The majority of the bleeding was at the site of venipuncture (22 patients) and was of no clinical significance Only one patient had a serious bleeding complication, autopsy evidence of hemorrhagic cerebral infarct possibly not related to SK A retrospective evaluation of this patient s file indicated a strong possibility of a pre infusion contraindication to thrombolytic therapy (transient ischemic attack history) which should have excluded him from the study Estimated blood loss was small in most cases Only one patient who received SK had a blood loss of greater than 250 c c No patient required transfusion replacement of blood lost with SK therapy The control group demonstrated a lower incidence of hemorrhagic complications with eight patients showing evidence of bleeding Of the control patients who had bleeding episodes eight received glucose and none was treated with heparin The difference in the total incidence of hemorrhagic complications between the SK group and control group was significant ($p < 0\ 0005$) There was no significant difference however in the number of patients who demon

Table IV Number of patients having temperature elevation during infusion

Temperature elevation	*SK*	*Control*
None	25 (47 1)	45 (83 3)
1 0-1 4 C	10 (18 9)	6 (11 1)
1 5-1 9 C	8 (15 1)	0 (0 0)
>2 0 C	6 (11 3)	1 (1 9)
Unknown	4 (7 6)	2 (3 7)

Table V Number of patients with allergic manifestations during infusion

Complication	*SK*	*Control*
Rash	3 (5 7)	0 (0 0)
Chills	9 (17 0)	0 (0 0)
Allergic reaction	3 (5 7)	1 (1 9)
Back pain	8 (15 1)	6 (11 1)
Tachycardia	19 (35 9)	11 (20 4)

strated a drop in hematocrit of greater than five points.

Another complication which has been reported frequently with SK therapy is elevation of body temperature during the infusion For the purposes of this report we have selected a temperature elevation of greater than 1 C as a clinically significant complication of SK As shown in Table IV 24 (45 3 per cent) out of 53 patients who received SK had a temperature elevation of greater than 1 C Six patients (11 3 per cent) had temperature elevations of greater than 2° C Only seven (13 per cent) out of 54 patients receiving the control infusion of 5 per cent glucose or heparin had a temperature elevation of greater than 1° C These differences are significant ($p < 0.0005$) There were no differences noted for the different SK preparations. Although the temperature elevation with SK is statistically significant, the febrile reactions presented no difficulty to the physicians responsible for the patient's care They were readily controlled by oral doses of 325 to 650 mg of acetaminophen every four to six hours or chlorpheniramine 10 mg intravenously We have examined our data to determine if the patients receiving SK with febrile reactions experienced more arrhythmia than patients receiving SK with no febrile reaction This correlation was sought to verify the clinical impression that the temperature elevations with SK are benign in view of the possibility that fever can induce arrhythmias. We were unable to demonstrate a correlation between SK induced fever and arrhythmia or tachycardia

Minor allergic reactions have also been reported with the infusion of SK in man [16] The foreign nature of SK and the presence of antibodies in many recipients may account for these reactions. In our series, as shown in Table V there was a slight increase in the number of patients with rash back pain or other manifestations of allergic reactions as compared with those patients receiving the control infusion These differences were not statistically significant There were no serious anaphylactoid reactions

The incidence of tachycardia (heart rate of greater than 100 per minute) was also followed as a complication of SK The association of tachycardia with fever cardiovascular distress, and allergic reactions makes its assessment as a complication of SK therapy difficult We observed that 19 out of 53 patients (35 9 per cent) receiving SK had tachycardia during the infusion as compared to 11 out of 54 patients (20 4 per cent) during the control infusion These differences were not statistically significant Whether the tachycardia resulted from the greater incidence of fever with SK the slight increase in allergic manifestations with SK or was another indication that the SK group had a more serious prognosis as indicated by the Peel scores is unanswered.

Cardiovascular complications which occur with considerable frequency in the setting of the coronary care unit were assessed to determine if SK influenced the incidence of these events These data are displayed in Table VI There was a slightly higher (but statistically insignificant) incidence of recurrent myocardial infarction angina friction rub congestive heart failure and shock in patients who received SK Control patients had a slightly increased rate of arrhythmia and phlebitis. None of these differences is of statistical significance This trend toward a greater number of cardiovascular complications in SK treated patients may also be a reflection of the higher risk of the SK group indicated by the Peel index for our sample We recognize that these cardiovascular complications are common features of myocardial infarction and may not be attributable to SK therapy

Each of the 107 patients accepted into the study was expected to receive an infusion for 24 hours Fifteen patients (14 per cent) of the total

Table VI Number of patients with cardiovascular complications during and after infusion

Complication	*SK*	*Control*
Recurrent MI	4 (7 6)	3 (5 6)
Angina	27 (50 9)	24 (44 4)
Friction rub	9 (17 0)	5 (9 3)
Heart failure	22 (41 5)	16 (29 6)
Shock	5 (9 4)	3 (5 6)
Tachycardia	19 (35 9)	11 (20 4)
Arrhythmia	40 (75 5)	41 (75 9)
Pulmonary embolism	1 (1 9)	1 (1 9)
Phlebitis	3 (5 7)	8 (14 8)

Table VII Premature termination of therapy

Treatment	*Length of infusion*		*Reason for termination*
Streptokinase	17 hrs	45 min	Bleeding
	3 hrs	35 min	Cardiac arrest
	3 hrs	8 min	Cardiac arrest death
	19 hrs		Pericarditis friction rub
	5 hrs		Friction rub
	1 hour	30 min	Toxicity −↑ BP nausea Choking sensation
	0 hrs		Pericardial rub never started infusion
	1 hour	30 min	Cardiac arrest death
	5 hrs	35 min	CVA signs
	18 hrs		Invasive procedure
		50 min	Pump malfunction
Glucose	5 hrs	35 min	Pericarditis
	3 hrs		Cardiac arrest
Heparin	21 hrs	10 min	Cardiac arrest death
	21 hrs	30 min	Pericardial rub

sample had their therapy terminated prematurely as shown in Table VII Eleven patients who were receiving SK and four patients with a control infusion had their infusion stopped This difference was not significant The principal reasons for premature termination were cardiac arrest (five patients) and evidence of pericardial inflammation (five patients) The infusion for two patients was terminated because of bleeding One of these patients had symptoms of a cerebrovascular accident possibly due to hemorrhage One infusion was terminated prior to a clinically indicated required invasive procedure and another infusion was terminated for an apparent toxic reaction There was also one instance of equipment failure responsible for an early termination of a therapeutic infusion

Ten collaborative clinical trials of the effect of fibrinolytic agents in acute myocardial infarction preceded our SMIT pilot study Of these studies nine employed SK as the thrombolytic agent and one used urokinase (UK) We have inspected the available data on six of the nine collaborative trials in which SK was used to compare the incidence of complications from therapy

Table VIII documents previous experience with hemorrhagic complications of SK Hemorrhagic complications ranged from 3 7 to 14 per cent The overall experience with hemorrhagic complications in the various trials was 7 9 per cent (101 out of 1,274 patients receiving SK) Three per cent of the patients receiving control infusions had hemorrhages (36 out of 1,197 patients) These reports of infrequent hemorrhagic complications contrast with our series in which 58 5 per cent of SK treated patients and 14 8 per cent of control patients had evidence of bleeding It is likely that our definition of a bleeding complication is more strict than in previous trials

Discussion

The SMIT pilot study was designed to provide the National Heart and Lung Institute with protocol and data collection experience to design a definitive trial of the efficacy of thrombolytic agents in acute myocardial infarction The pilot study was concluded when a sufficient number of patients was accessed to test the feasibility of a larger definitive trial

The SMIT pilot study demonstrated that 42 out of 53 (79 2 per cent) patients receiving SK had at least one of three complications hemorrhage temperature elevation, or allergic manifestation Only 14 out of 54 (25 9 per cent) of control patients had a complication This high incidence of untoward reactions with SK was alarming until further investigation of the data was undertaken Total hemorrhagic complications of 58 5 per cent of patients treated with SK appears to be much higher than previous reports of 3 7 to 14 per cent This discrepancy probably reflects our definition of very minor bleeding as a complication Twenty two patients bled only from puncture sites The only serious bleeding complication was a hemorrhagic cerebral infarct in one patient probably accepted for study in error No transfusions were required, and a hematocrit drop of five points or more was noted equally in patients on SK and in control patients

While 24 out of 53 patients had a temperature

Table VIII Hemorrhagic complications of streptokinase in myocardial infarction

	1st EWP		*2nd EWP*		*1st Gr-Sw*		*2nd Gr-Sw*		*Italian*		*Finnish*	
	SK	*Hep*	*SK*	*Hep*	*SK*	*Hep*	*SK*	*Glu*	*SK*	*Hep*	*SK*	*Glu*
	83	84	373	261	297	261	138	131	164	157	219	207
Overall	9	4	32	7	9	0	14	10	23	12	12	3
	(10 8%)	(4 8%)	(8 6%)	(2 0%)	(3 0%)	(0 0%)	(10 1%)	(7 6%)	(14 0%)	(7 6%)	(5 5%)	(1 5%)
Puncture site	2	1			6		1	0	1	0	2	0
Genitourinary	1				1		4	6	16	7	7	3
Gastrointestinal	1	2			1		2	2	0	2	1	0
Hematoma	2								0	0		
Intracranial									0	0		
Hemoptysis		1					2	0	3	3		
Epistaxis	2						4	1	3	0		
Gingival							1	1			2	0
Unspecified	1				1							

elevation of greater than 1° C during SK infusion as compared to 7 out of 54 receiving control infusion management of these febrile reactions was not a clinical problem Clinicians using presently available preparations of SK should expect a benign self limited febrile reaction to occur in about 50 per cent of the patients We were unable to demonstrate that these fevers increased the incidence of potentially malignant arrhythmias or had any measurable adverse effect on the patients. The possibility that increased oxygen demands from fever may increase cardiac muscle damage and thus lead to a higher incidence of congestive heart failure or aneurysm should be considered.

There was a slight increase in allergic manifestations among SK treated patients Rash chills pruritis and back pain were no problem in patient management however There were several types of cardiovascular complications which were slightly more frequent in the SK group These trends may have resulted from the randomization inequities which distributed more high risk patients to SK than to control The higher incidence of friction rubs in patients receiving SK than control (nine as opposed to five) is of potential concern but not of statistical significance in our present series

The data demonstrate a relatively large difference in the percentage of patients with febrile reactions and minor hemorrhagic complications in SK treated patients as compared with control patients Allergic manifestations were noted but with smaller differences Cardiovascular complications were about the same in both groups Despite the relatively benign nature of the complications observed, the incidence of undesirable events in patients receiving SK therapy was higher than previously reported in earlier clinical trials The question of whether apparently benign complications such as fever or minor bleeding can lead to the life threatening complications of arrhythmia or shock remains to be clarified. The risk/benefit ratio of SK therapy in patients having low risk of death with conventional therapy must be considered in relation to both future clinical trials and widespread application of thrombolytic therapy Patients with a low risk of mortality will not contribute to the attainment of statistical significance in a mortality endpoint trial The potential risks of SK may be greater than the potential benefits to this particular group of patients Therefore for two reasons low risk patients with myocardial infarction should probably be excluded from any definitive trial of SK therapy in reducing mortality in acute myocardial infarction This interdiction might not apply to trials of urokinase or to the therapeutic use of a proved drug

A third area of concern raised by data from the SMIT pilot study is the modified double blind nature of any trial of SK in acute myocardial infarction Although the investigators who were responsible for the decisions concerning patient care were to be kept blind, the incidence of bleeding or fever in these patients probably made it relatively easy for an aware observer to determine what therapy the patient was receiving The ease of distinguishing SK patients from control patients may account for the premature ter

mination of therapy in eleven patients receiving SK as opposed to only four patients with the control infusion. Knowledge of the therapy may have consciously or subconsciously biased investigators to look with greater care for indications to terminate the SK infusion.

Even though the SMIT pilot study made no attempt to settle the issue of the efficacy of SK in lowering mortality in myocardial infarction, the data it produced may aid in the design of a study which can accomplish that goal. An awareness of the incidence of complications may help physicians using SK for other conditions. It is clear from the pilot data that the ramifications of minor complications and difficulty in blinding investigators must be clarified before a universally acceptable definitive trial can be completed.

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Reproducibility of the angiographic left ventricular ejection fraction in patients with coronary artery disease*

Peter F Cohn MD
Jay A Levine MD
Gary A Bergeron MD
Richard Gorlin MD
Boston, Mass

The left ventricular systolic ejection fraction has proved to be a useful measurement in assessing the degree of cardiac decompensation in patients with both primary and secondary forms of myocardial disease [1-10] The high degree of reproducibility of ventricular volumes obtained from sequential beats in the same ventriculogram has been reported by several investigators [11,12] What has not been resolved is (1) the reproducibility in the same patient of ventricular volumes (and derived ejection fractions) obtained from either separate day ventriculographic studies or from ventriculograms performed before and after coronary arteriography or from ventriculograms obtained by either left ventricular or pulmonary artery injections of contrast medium as well as (2) the inter observer variation in the analysis of the same ventriculographic silhouettes By addressing itself to these issues, this study attempts to provide a frame of reference for the analysis of sequential left ventriculograms performed in a given patient with coronary artery disease

Materials and methods

Patient selection This study included 20 patients with coronary artery disease who were in regular sinus rhythm at the time of their cardiac catheterizations All patients gave informed consent for the repeat ventriculographic studies Excluded from the study were patients with ventricular dysfunction severe enough to contraindicate multiple ventriculographic procedures

The patients were divided into three groups depending on the time and site of the repeat ventriculographic study The five patients in Group 1 had a repeat study before coronary arteriography and approximately *30 minutes* after the first ventriculogram to minimize residual hemodynamic effects of the preceding dose of contrast medium [13-15] The 10 patients in Group 2 had a second study approximately *90 minutes* after the initial ventriculogram and at least 30 minutes after the conclusion of coronary arteriography (All 10 patients received 1/300 grains of sublingual nitroglycerin approximately 60 minutes prior to the repeat study) Five of the 10 patients had the repeat study performed by injection of contrast into the left ventricle (Group 2A) the other five patients by injection into the main pulmonary artery (Group 2B) The five patients comprising Group 3 had a second study *more than 24 hours later* (from two to four days) after the first These patients required additional coronary arteriography and the repeat ventriculograms were performed immediately before that procedure (Precatheterization medication was the same on both days)

Cardiac catheterization Standard hemodynamic parameters were determined in all patients Thus cardiac rate systemic systolic pressure and left ventricular end diastolic pressure (LVEDP) were obtained prior to both the initial

From the Cardiovascular Division Department of Medicine Peter Bent Brigham Hospital and the Department of Medicine Harvard Medical School, Boston, Mass

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Reprint requests to Dr Peter F Cohn, Department of Medicine Peter Bent Brigham Hospital, 721 Huntington Ave Boston, Mass 02115

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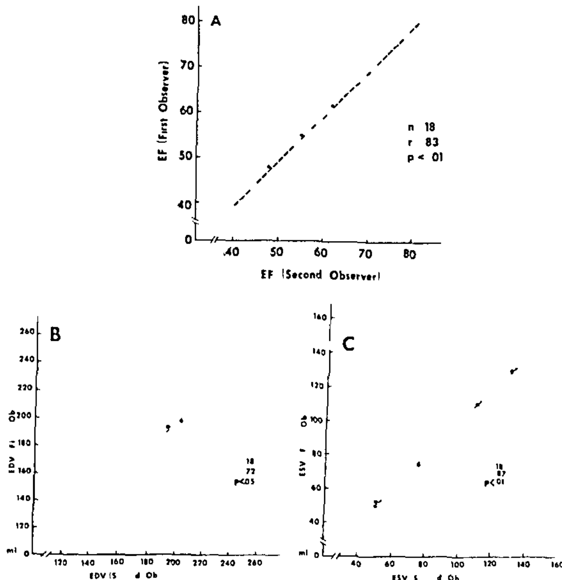


Fig 1 Inter observer variation in determining *A* ejection fractions (EF) and *B* and *C* end diastolic and end systolic volumes (EDV and ESV) from the same ventriculographic silhouettes.

and repeat ventriculographic studies in all patients save for the five patients in Group 2B In these five patients pulmonary artery diastolic pressure was measured prior to both studies since the angiographic catheter was in the pulmonary artery rather than the left ventricle for the repeat ventriculogram Cardiac output was determined by the green dye dilution technique in all patients prior to the initial ventriculogram and in 14 patients prior to the repeat study

Angiography The initial left ventriculogram was obtained with a Cordis pigtail catheter positioned in the left ventricle Forty to 50 ml of 76 per cent meglumine sodium diatrizoate was injected over a three to four second period using a Viamonte power injector The same technique was employed for the repeat study, except that in five patients (Group 2B) an Eppendorf catheter was positioned in the main pulmonary artery and 50 to 60 ml of 76 per cent meglumine sodium diatrizoate was injected over a three to four second period (The purpose of the extra amount of contrast medium was to attain cine resolution comparable to the initial study using a left ventricular injection) All ventriculograms were recorded at 60 to 100 frames per second on 16 mm cine film By setting the rotating cradle at an angle of 30 degrees in the right anterior oblique projection and by measuring the distances from the camera to the chest to the table top patients could readily be placed into their original radiographic positions for the repeat ventriculogram

Assuming the ventricle to be ellipsoidal the area length method of Dodge and Baxley[1] was used to determine end diastolic and end systolic volumes (EDV and ESV) The manually drawn angiographic silhouettes were calibrated to life

size via a filmed grid of known dimensions Ejection fraction was calculated by the formula

$$\text{Ejection fraction} = \frac{EDV - ESV}{ESV}$$

For purposes of standardization the first beat in each ventriculogram was defined as that beat immediately following complete opacification with contrast medium In the present study only beats one two or three were analyzed, and ventricular premature contractions and subsequent beats were purposefully not considered However no patients had to be excluded because of multiple premature contractions

The term asynergy was used to define any abnormalities of wall motion in the anterior apical or inferior zones as described by Herman and Gorlin [16]

Coronary arteriography was performed using the Judkins technique

Results

Inter observer variations in determining ejection fractions The following conventions were followed in drawing angiographic silhouettes the largest silhouette was considered end diastole the smallest end systole The latter included the outer border of the papillary muscles although resolution in this region is not always optimum Using these conventions each investigator independently analyzed the ventriculograms

When the same 18 beats were analyzed by two different observers there was no statistically significant difference between EDV (198 ml $\pm$ 9 vs 197 ml $\pm$ 9*) ESV (84 ml $\pm$ 5 vs 81 ml $\pm$ 5) or ejection fraction (0 60 $\pm$ 0 03 vs 0 58 $\pm$ 0 03) There was no systematic difference between the values obtained by either observer The range of ejection fractions between the first and second observer was −0 07 to +0 10 with an average difference of 0 05 (Fig 1 *A*) (The latter value was determined by the arithmetic mean of the absolute numerical difference in ejection fractions without regard to sign) Average difference in EDV was 20 ml and in ESV 10 ml (Fig 1 *B* and *C*)

Beat to beat variations within the same ventriculogram Eighteen pairs of consecutive beats were analyzed with each beat of the pair analyzed by the same observer Again there was no systematic or statistically significant difference between EDV (185 ml $\pm$ 8 vs 184 ml $\pm$ 9) ESV (75 ml $\pm$ 6 vs 74 ml $\pm$ 7) or ejection fraction (0 59 $\pm$ 0 03 vs 0 60 $\pm$ 0 02) The range from one beat to the next was −0 04 to +0 03 with an average difference of 0 02 (Fig 2 *A*) Average difference in EDV was 6 ml and in ESV 4 ml (Fig 2 *B* and *C*)

Variations between sequential ventriculograms There was no statistically significant difference in heart rate (74 beats per minute $\pm$ 6 vs 71 beats per minute $\pm$ 5) systemic systolic pressure (124 mm Hg $\pm$ 5 vs 117 mm Hg $\pm$ 7) ventricular filling pressure—LVEDP or pulmonary artery diastolic pressure—(9 mm Hg $\pm$ 1 vs 9 mm Hg $\pm$ 1) or cardiac output (5 6 liters per minute $\pm$ 0 3 vs 5 9 liters per minute $\pm$ 0 4) obtained prior to the sequential studies Average differences were 10 beats per minute (heart rate) 10 mm Hg (systemic systolic pressure) and 2 mm Hg (LVEDP or pulmonary artery diastolic pressure) and 0 6 liter per minute (output)

There was no statistically significant difference between volumes and ejection fractions determined from the same beat* in sequential ventriculograms in these 20 patients (EDV 189 ml $\pm$ 11 vs 180 ml $\pm$ 9 ESV 75 ml $\pm$ 5 vs 68 ml $\pm$ 6 and ejection fraction 0 60 $\pm$ 0 04 vs 0 63 $\pm$ 0 04) There was a random variance of volumes and ejection fractions between the sequential studies with the most scatter occurring in Groups 2 and 3 The range in ejection fraction from the first to the second study was − 0 15 to + 0 20 with an average difference of 0 07 (Fig 3 *A*) Average difference in EDV was 27 ml and in ESV 21 ml (Fig 3 *B* and *C*) The variations within the individual groups are as follows (pNS unless otherwise noted)

Group 1 (30 minute interval) In these five patients the average difference in ejection fraction between sequential studies was 0 04 Average difference in EDV was 19 ml and in ESV 17 ml

Group 2 (90 minute interval) In the five patients in Group 2A the average difference in ejection fraction was 0 04 Average difference in EDV was 20 ml and in ESV 14 ml

In the five patients in Group 2B resolution of the cardiac borders was noted to be less precise following the second (pulmonary artery) ventric

M n ± standard error of the m n.

If tw observers n lyzed this be t, th aver ge value of the two was used in th part of the study

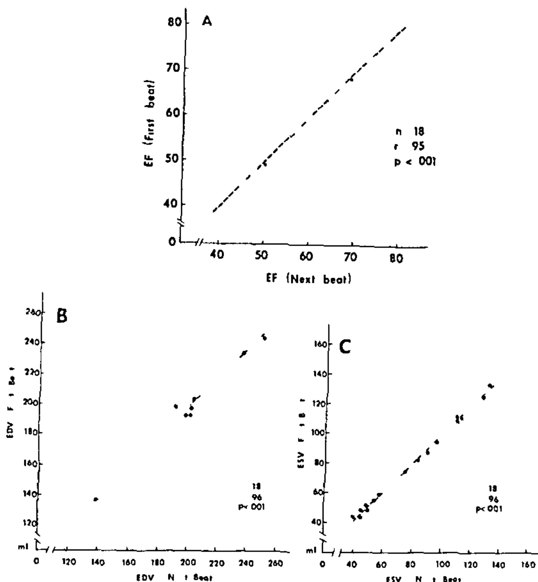


Fig 2 Beat to beat variation in *A* ejection fractions (EF) and *B* and *C* end diastolic and end systolic volumes (EDV and ESV)

ulogram compared to the initial ventriculogram performed by intraventricular injection Average difference in ejection fraction was 0 08 Average difference in EDV was 50 ml and ESV 22 ml EDV after pulmonary artery injection was significantly higher than after ventricular injection (Fig 3*B* 208 ml ± 15 vs 166 ml ± 11 p < 0 05)

Group 3 (> 24 hour interval) In these five patients the average difference in ejection fractions between sequential studies was 0 13 Ejection fractions were significantly higher in the repeat study (69 ± 0 04 vs 62 ± 0 03 p < 0 05) Average difference in EDV was 20 ml and in ESV, 32 ml

Possible mechanisms for the variances noted above are considered at length in the following section and in the Discussion

Analysis of individual patients with variations in ejection fraction > 0 10 Six of the 20 patients had differences in ejection fractions > 0 10 One patient was in Group 2A, one in Group 2B and four in Group 3 When coronary artery and wall motion abnormalities in these six patients were compared to abnormalities in the other 14 patients no appreciable difference was found (Table I) However, five of the six patients in this category had larger than average differences in one or another of the hemodynamic measurements noted earlier compared to only three of the other 14 patients (p < 0 05) Representative of the five patients was JR (Group 2B) with an ejection fraction of 0 62 on his first study, and 0 47 on the second study performed at the conclusion of the catheterization Heart rate increased from 65 to 90 beats per minute and systemic systolic pressure decreased from 154 to 120 mm Hg Pulmonary artery diastolic pressure increased from 10 mm Hg to 13 mm Hg and cardiac output was

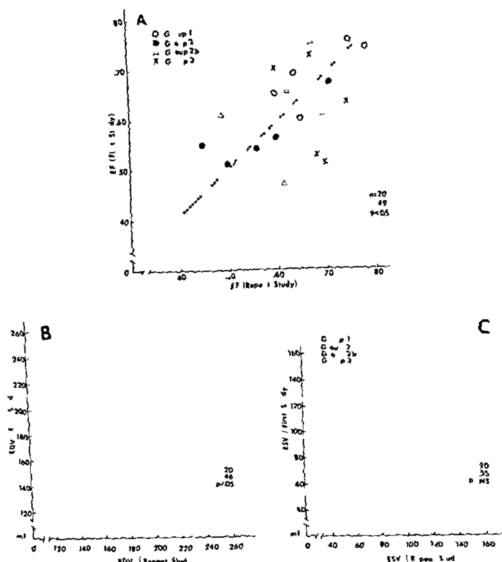


Fig 3. Inter study variation in *A* ejection fractions (EF) and *B* and *C* end diastolic and end systolic volumes (EDV and ESV) The most scatter occurred in Groups 2 and 3

unchanged Apical asynergy was more pronounced on the repeat study in this patient with obstructive disease of the left anterior descending and right coronary arteries. The other (sixth) patient in this category (patient RR in Group 3) had an ejection fraction of 0 52 on his initial study that increased to 0 68 on his repeat study three days later while heart rate pressures and cardiac output were essentially unchanged. Apical asynergy was more pronounced on the initial study in this patient with obstructive disease of the left anterior descending and right coronary arteries. In none of the six patients were acute signs or symptoms of myocardial ischemia present prior to either ventriculogram

Discussion

Determination of the intrinsic range of variation of the left ventricular ejection fraction is a necessary prerequisite for the clinical use of this hemodynamic measurement. Thus reports that myocardial revascularization procedures improve ventricular function as evidenced by higher ejection fractions postoperatively[17-20] may need to be reconsidered in light of the present data We have demonstrated that the average difference in ejection fraction was 0 07 between matched beats of sequential cine left ventriculograms filmed in the right anterior oblique position during comparable hemodynamic states i e similar mean values for heart rate systemic ar

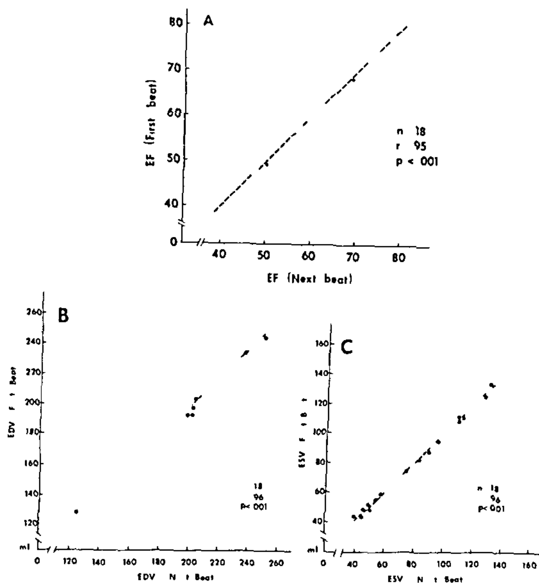


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vantage of a lower frequency of extrasystoles than direct ventricular injection despite lesser definition of cardiac chambers.

In conclusion this study has demonstrated an average difference of 0 07 in manually determined ejection fractions from one cine study to the next in the same patients at comparable hemodynamic states as determined by readily obtainable standard diagnostic parameters These data emphasize the necessity of determining the hemodynamic state at the time of ventriculography especially when evaluating results of medical or surgical therapy (1) if the hemodynamic states are comparable from one study to the next, small differences in volumes and ejection fractions (i.e < 0 07) may represent only the intrinsic range of variation of this parameter (2) If the hemodynamic measurements differ markedly from the average changes observed in sequential studies—as suggested by our group of 20 patients—no meaningful conclusions can be drawn concerning the effect of medical or *surgical therapy on the* ventricular volumes or ejection fraction in patients with coronary artery disease This is because these values are influenced directly by hemodynamic variables such as heart rate preload afterload and contractile state as well as by myocardial ischemia and indirectly by the time between studies Whether or not sequential studies are done before or after arteriography (with or without nitroglycerin administration) also must be taken into account as should the site of the contrast medium injection (left heart *vs right heart)* Finally inter observer differences may introduce another variability factor and should be controlled whenever possible by standardized procedures for analysis of ventriculographic silhouettes

Summary

Quantitative analysis of the single and repeated cine left ventriculogram was performed in 20 patients with coronary artery disease to determine both the intrinsic variance of individual beats separated by different time intervals and variance between analyses of different observers In addition ventriculograms obtained from left ventricular injections of contrast medium prior to coronary arteriography were compared to ventriculograms obtained from either left ventricular or pulmonary artery injections after arteriography The time period between studies varied from 30 minutes to 90 minutes to four days Analysis of the same ventriculogram by different observers resulted in an average difference in ejection fraction of 0 05 (pNS) The average difference in ejection fraction was 0 02 between two early beats of the same ventriculogram (pNS) The average difference between sequential ventriculograms was 0 07 (pNS), but individual variations greater than 0 10 were not uncommon particularly between studies done before and after arteriography or several days apart Patients exhibiting wide variance in ejection fractions between two studies either had wide variance in other hemodynamic measurements or degree of asynergy or both This study provides a frame of reference for analysis of sequential ventriculograms in patients with coronary artery disease especially in evaluating changes in the state of the disease or the effects of therapy It is especially important that (1) standard hemodynamic measurements be made before ventriculography (2) the same radiographic techniques repeated whenever possible and (3) the same person analyze the two ventriculograms

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Table I Correlations between angiographic findings and variations in ejection fractions

Δ EF from first to second study	Coronary arteries diseased		Zones of asynergy*		
	Single	Multiple	None	Single	Multiple
>0 10 (n = 6)	2	4	1	2	3
<0 10 (n = 14)	4	8	3	5	6

* Initial ventriculogram
EF = ejection fraction

terial pressure, LVEDP, and output Since most ejection fractions were in the 0 50 to 0 70 range, this represents *a variation of 10 to 15 per cent* A previous study has demonstrated that differences in ejection fraction also exist between single plane and biplane cine techniques in the same patient Although also not statistically significant this difference averages 0 08 in patients with asynergy and asymmetrically contracting ventricles [21]

Difference in ejection fractions from one study to the next in the same patient may be due to several factors the first of which is *cine resolution* This is most troublesome with pulmonary artery injections even with the use of larger amounts of contrast agent than usual Second is *intra observer variation*. This is probably not significant since the reproducibility of ejection fractions from one beat to the next in the same ventriculogram is excellent if the same investigator draws and analyzes the silhouettes (Fig 2) However *inter observation variation* may occasionally result in sizable differences in derived data (Fig 1) It is preferable that (1) the same observer calculate sequential ejection fractions whenever possible or at least (2) that standardized conventions are adopted and strictly adhered to if different observers are involved Hopefully the use of automated techniques for determining ventricular volume[22 23] will reduce this potential source of human error Another reason for variation in ejection fractions between sequential ventriculograms is the *difference in the hemodynamic state* Hemodynamic measurements obtained in man up to 30 seconds after infusion of angiographic contrast medium into the left atrium, left ventricle or pulmonary artery are largely unchanged from the pre infusion state [11 24] Thus ejection fractions derived from angiographic ventricular volumes probably reflect the immediate pre infusion state for that study If systemic pressure LVEDP (as a crude index of EDV), heart rate or contractile state change this can affect the ejection fraction For example, a primary change in inotropic stimulation will increase the ejection fraction while augmented impedance (increased blood pressure) would decrease it Increases in LVEDP (EDV) or heart rate may have variable effects In addition when calculated from end diastolic and end systolic angiographic silhouettes ejection fraction is obviously affected by the shape of the ventricle, and ventricular geometry has been demonstrated to alter dramatically following experimental changes in preload and afterload [25] Changes in the hemodynamic state may also precipitate myocardial ischemia in an area subserved by an obstructed coronary artery resulting in both abnormal regional wall contraction and a depressed ejection fraction Conversely it is possible that transient localized asynergy may be the cause rather than the effect of a depressed hemodynamic state, and at times asynergy may be present without obvious hemodynamic changes It would be expected that the greater the time between the sequential studies (once the initial effects of the dye have been dissipated) the more likelihood that there would be changes in hemodynamic state and/or myocardial perfusion This premise is borne out by the finding that the only significant difference in ejection fractions in the present study occurred in Group 3 Finally differences in ejection fractions must be related to *changes in either EDV or ESV*, or both since the ejection fraction is a function of the two volumes In most instances in the present study changes in both of these measurements were present when the ejection fraction differed from one study to the next or from one observer to another These changes did not achieve statistical significance however The one exception occurred when the ventriculograms following the pulmonary artery injections were compared to those with left ventricular injections The larger EDV often observed after the left ventricular injection may be related to transient mechanical distention of the chamber or to a decreased cine resolution of left ventricular borders from the pulmonary artery injection as noted earlier This is an important consideration since the pulmonary artery injection has the ad

Blood levels of lidocaine following subcutaneous administration prior to cardiac catheterization

Mortimer L Schwartz M D
Benjamin G Covino Ph D M D
Ravinder M Narang M D
Virender Sethi M D
Sudama S Tholpady M D
Manoch Kuangparichat M D
Catherine Giordano R N
Melvin B Meyer M D
Bronx, N Y

Lidocaine has been employed for many years as a local anesthetic agent for a variety of regional anesthetic procedures. In recent years lidocaine has also been extensively used intravenously for the treatment and prevention of ventricular arrhythmias—particularly those associated with acute myocardial infarction[1] Numerous studies have been performed in which blood levels of lidocaine have been determined following various regional anesthetic procedures[2,3] and following its use intravenously as an antiarrhythmic agent[1] In addition studies in animals and man have been carried out in an attempt to correlate the blood levels of lidocaine with both its antiarrhythmic activity and its toxicologic effects Previous reports have suggested that blood levels of approximately 1 5 μg per milliliter are required to achieve antiarrhythmic activity whereas blood levels generally must exceed 5 μg per milliliter before side effects of a central nervous system (CNS) and cardiovascular nature are observed[1]

Lidocaine is commonly employed for infiltration anesthesia in patients undergoing cardiac catheterization for the minor surgery required for the insertion of catheters into peripheral arteries and/or veins. No information is available concerning the blood levels of lidocaine which are achieved following its subcutaneous administration for this purpose Scott and co workers[3] did report a mean maximum plasma level of lidocaine of 1 95 $\pm$ 0 23 μg per milliliter following the subcutaneous administration of 400 mg of lidocaine in the abdomen Thus the following study was conducted in an effort to determine whether the blood levels of lidocaine achieved are such that they might provide a degree of ventricular antiarrhythmic effectiveness during the catheterization procedure or whether the levels might be sufficiently high to produce hemodynamic changes which could alter the diagnostic value of the measurements obtained during cardiac catheterization

Methods

The procedure employed for cardiac catheterization at the Bronx Lebanon Hospital Center involves the subcutaneous administration of 200 mg (10 ml of 2 per cent) lidocaine into the antecubital fossa Infiltration is completed within 60 seconds Following the onset of local anesthesia in this area normal minor surgical procedures are performed for the isolation of the brachial artery and one or more antecubital veins and subsequent placement of cardiac catheters via either the arterial or venous system

Eight subjects five males and three females were selected for the study All patients were scheduled for routine right and left cardiac catheterization and/or coronary angiography Blood

From th Cardiovascula Section, Department of Medicine The Bronx Lebanon Hosp tal C nter Bronx, N Y and the Med cal Department, Astra Pharm ceutical Prod cts I c W rcester M ss.
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Rept nt requests to: Dr M. L. Schw rtz Chief f Cardiology Bronx Lebanon Hosp tal Center 1276 Fulton Ave Bronx, N Y 10456

Jr Behar V S Peter R H Rosati R A Young W G Jr and Sabiston D C Jr Risk factors in coronary artery bypass surgery Arch Surg 105 918 1972
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From the Cardiovascular Section Department of Medicine The Bronx Lebanon Hospital Center Bronx, N Y and the Medical Department, Astra Pharmaceutical Products Inc Worcester Mass
Received for publication March 19 1974
Reprint requests to Dr M L. Schwartz Chief of Cardiology Bronx Lebanon Hospital Center 1276 Fulton Ave Bronx, N Y 10456

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rious effects particularly of a cardiovascular nature and should not affect the hemodynamic data obtained during cardiac catheterization

Summary

Blood levels of lidocaine were determined in eight subjects in whom 200 mg of lidocaine were administered subcutaneously for infiltration anesthesia in preparation for cardiac catheterization studies The results indicate that mean peak levels of 0 28 to 0 49 μg per milliliter were obtained during a two hour period following lidocaine administration In view of the extremely low levels of lidocaine observed in this study the results indicate that no alteration of hemodynamic function should occur following the use of lidocaine in this manner In addition one should not anticipate any degree of ventricular antiarrhythmic activity due to the low levels of lidocaine achieved

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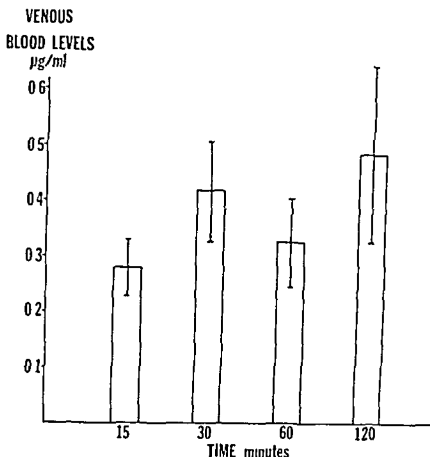


Fig 1 Mean ± S E venous blood levels of lidocaine following the subcutaneous administration of 200 mg of lidocaine to eight patients undergoing cardiac catheterization

samples were taken from the antecubital vein of the arm opposite to that in which infiltration anesthesia was performed Samples were obtained just prior to the administration of lidocaine and at 15 30 60 and 120 minutes following the administration of lidocaine Lidocaine levels were measured by a gas chromatographic technique similar to that described by Keenaghan [4] Whole blood was utilized for the determination of lidocaine and the lidocaine values were expressed in the form of lidocaine base

Results and discussion

Fig 1 is a bar graph which presents the mean whole blood lidocaine concentrations obtained in the eight subjects following subcutaneous administration of 200 mg of this agent As can be seen the peak mean blood levels of lidocaine obtained in the various subjects varied from 0 28 ± 0 05 µg per milliliter to 0 49 ± 0 16 µg per milliliter The graph also indicates the relatively slow rate of absorption of lidocaine from the subcutaneous injection site In general peak levels tended to occur at 30 minutes There appeared to be a secondary peak at 120 minutes but this was due to one subject who had 1 4 µg per milliliter at that time period

In terms of possible antiarrhythmic effectiveness it had been shown that levels of lidocaine of approximately 1 5 µg per milliliter are required for antiarrhythmic activity [1] Indeed, we have demonstrated quite a good correlation between blood levels of lidocaine and frequency of ventricular premature beats [5] The results obtained in this study would indicate that the blood levels of lidocaine achieved following the subcutaneous administration of 200 mg are not sufficient to provide any significant degree of antiarrhythmic activity

In terms of potential toxicity the data also indicate that the blood concentration of lidocaine achieved by the subcutaneous administration of 200 mg is far below that which is believed necessary for side effects to occur (> 5 0 µg per milliliter) Hemodynamic studies have indicated no alteration in cardiovascular properties with levels of lidocaine in excess of those observed in this study Thus the use of 200 mg of lidocaine for infiltration anesthesia should not have delete

Table I Subjects investigated

	Normal subjects		BLH			FEH			HEH		
	Mean	S.E	Mean	S.E	p*	Mean	S.E	p*	Mean	S.E	p
Age (years)	25	(1 3)	30	(1 9)	<0 1	44	(2 0)	<0 001	47	(2 9)	<0 001
Sex M F	14 3		22 7			13 3			5 4		
DP (mm Hg)	79	(1 4)	86	(2 4)	<0 05	111	(4 0)	<0 001	122	(7 1)	<0 001
HR (beats/min.)	69	(2 3)	77	(2 2)	<0 025	72	(2 5)	n.s	86	(6 1)	<0 005

BLH borderline hypertension FEH fixed established hypertension HEH hyperkinetic established hypertension SE standard error and DP diastolic blood pressure

p refers to statistical significance of difference from normal subjects

Table II Systolic time intervals in all hypertensive patients regardless of type

	Normal subjects		Hypertensive patients		p
	Mean	S E	Mean	S E	
PEP (msec)	104	(2 8)	105	(2 6)	n s
IVCP (msec)	38	(1 2)	38	(2 2)	n s
LVET (msec)	405	(3 9)	410	(2.9)	n s
PEP/LVET	0 355	(0 013)	0 372	(0 011)	n s.
DP /IVCP (mm. Hg/sec)	2 116	(78)	3 045	(194)	<0 005

S E stands d error

pressure and evidence of a hyperkinetic heart were constant in this group

2 Sixteen patients with fixed established hypertension (FEH) were characterized by persistent elevation of diastolic pressure (more than 90 mm Hg) with minimal variability and no evidence of a HEH

3 Patients with established hypertension and a HEH there were nine patients who had persistent diastolic hypertension associated with a HEH and excessive variability of arterial pressure Although their average diastolic blood pressure was higher than the second group the difference was not statistically significant (Table I)

The electrocardiogram of each patient was reviewed. All had a regular sinus rhythm without evidence of left or right bundle branch block The diagnosis of left ventricular hypertrophy was based on the criteria of McPhie[†] All patients had all medications discontinued for at least one month prior to study

For measurement of systolic time intervals (STI) the standard limb lead which inscribed the earliest QRS deflection (usually Lead II) was selected to define the onset of ventricular depolarization Simultaneous indirect carotid artery pulse tracings external phonocardiogram and electrocardiogram were recorded on photographic paper at a speed of 100 mm per second with time lines of 10 msec The carotid pulse was obtained with a Hewlett Packard piece (ATP 16) held manually over the right common carotid artery Heart sounds were recorded with a Sanborn dynamic microphone from the precordial area giving the clearest inscription of the high frequency vibrations of the first and second heart sounds this was generally in the fourth left parasternal space or inside the point of maximal cardiac impulse The low cutoff frequencies of the phonocardiographic filters were set at 50 Hz Recordings were made in all subjects in the postabsorptive state at rest in the supine position The procedure was explained in advance and the recordings obtained in a quiet isolated room where admissions were limited. A sphygmomanometer cuff was applied to the patient s arm and arterial pressure was checked every five minutes Diastolic blood pressure was taken as the fourth phase of Korotkoff s sounds Recordings were started when at least three consecutive arterial pressure measurements were almost

[†]The greatest R in any precordial lead plus the deepest S in any precordial lead > 43 mm.)

Cardioadrenergic factor in essential hypertension

M Mohsen Ibrahim, M D
Robert C Tarazi, M D
Harriet P Dustan, M D
Emmanuel L Bravo M D
Cleveland Ohio

An active cardiac contribution to hypertension has often been postulated but not yet clinically verified Increased cardiac output in borderline and mild hypertension has been well recognized[1 3] less well known but occasionally quite impressive is its incidence in a minority of patients with chronic sustained hypertension However, a high output does not necessarily imply increased cardiac contractility[4] because of the many factors that help determine the level of output In the absence of more direct indices of myocardial contractility it is not possible to speculate on cardiac performance in hypertensive patients on the basis of cardiac output determinations alone Direct intraventricular studies would be difficult to obtain in a large group of asymptomatic patients and when such studies are available results have been questioned on the grounds that the hemodynamic status may have been altered by premedication or the associated anxiety of the procedure

Measurement of systolic time intervals offers a good opportunity to assess cardiac contractility and adrenergic function at the bedside There is rapidly accumulating evidence to indicate that these intervals provide a valid assessment of the contractile state of the left ventricular myocardium in man[5] The lengths of pre ejection (PEP) and isovolumic contraction periods (IVC) and their response to beta adrenergic blockade serve in addition as useful criteria of adrenergic influences on cardiac dynamics[6]

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Reprint requests Dr Robert C Tarazi Research Division Cleveland Clinic 9500 Euclid Ave Cleveland, Ohio 44106

The present study was undertaken to investigate cardiac contractility and adrenergic functions as measured by systolic time intervals in three groups of patients with essential hypertension

The results indicate that an excessive cardioadrenergic drive is present not only in borderline cases, but also in some patients with established hypertension

Methods

Indirect systolic time intervals were measured in 54 patients with essential hypertension and in a control group of 17 normal subjects All had complete clinical and laboratory evaluation including intravenous pyelography—renal arteriography was performed when indicated None of the patients had cardiac or renal decompensation or valvular heart disease Variations in arterial pressure were determined both from records of the referring physician and from at least one week of six hourly measurements in the hospital Patients with fluctuation of 50 mm Hg or more in systolic pressure were described as having excessive variability of blood pressure The following were taken as evidence of hyperkinetic heart (HEH) history of inappropriate tachycardia and excessive palpitation either spontaneously or in relation to exertion meals or emotion, together with a hyperactive cardiac impulse Based upon the level of arterial pressure its degree of fluctuation, and the presence or absence of clinical manifestations of hyperkinetic heart, patients were classified into three homogeneous groups (Table I)

1 Twenty nine patients with borderline hypertension (BLH) defined as those who had a diastolic pressure below 90 mm Hg on more than one occasion Excessive variability of arterial

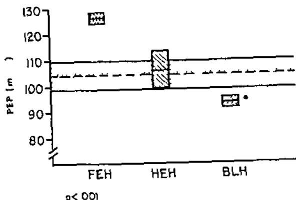


Fig 1 PEP in the three groups of hypertensive patients investigated in this as in subsequent figures the values derived from 17 normotensive subjects *are indicated* by the horizontal line and the standard error by the shaded area The vertical blocks represent averages and S E in milliseconds in each of the groups (FEH = 126 ± 1 9 HEH = 106 ± 6 7 and BLH = 93 ± 2 1) p refers to the statistical significance of differences between normal and hypertensive groups FEH fixed established hypertension HEH hyperkinetic established hypertension and BLH borderline hypertension.

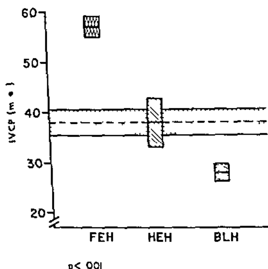


Fig 2 IVCP in the three groups of hypertensive patients (FEH = 57 ± 2 3 HEH = 38 ± 4 9 and BLH = 28 ± 1 7) Abbreviations as in Fig 1

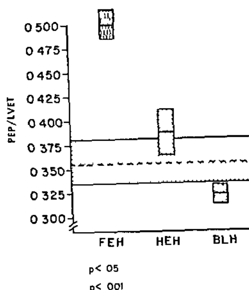


Fig 3 PEP/LVET in the three groups of hypertensive patients (FEH = 0 499 ± 0 016 HEH = 0 391 ± 0 022 and BLH = 0 323 ± 0 009) Abbreviations as in Fig 1

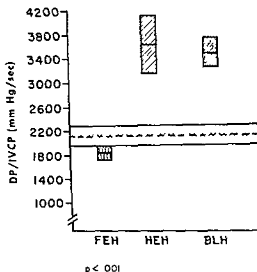


Fig 4 The rate of rise of ventricular pressure was estimated from the ratio of diastolic pressure at the time of recording to the IVCP (DP/IVCP) and expressed as millimeters of mercury per second. (FEH = 1 862 ± 113 HEH = 3 651 ± 497 and BLH = 3 484 ± 257) Abbreviations as in Fig 1

Spontaneous fluctuations of arterial pressure Repeated studies allowed recording of STI in seven patients at different levels of pressure spontaneous rises of arterial pressure (diastolic averaging 12 mm Hg p < 0 01 systolic averaging 26 mm Hg p < 0 001) were generally associated with acceleration of heart rate shortening of PEP and IVCP prolongation of LVET elevation of DP/IVCP and reduction of PEP/LVET (Fig 5) However only changes in PEP (p < 0 05) LVET (p < 0 05) and PEP/LVET (p < 0 05) were significant LVET changed from 400 ± 7 to 414 ± 7 6 msec

Effect of propranolol Propranolol decreased heart rate by 12 ± 2 beats per minute in patients with BLH and by 10 ± 2 in those with FEH patients with HEH had the most impressive slowing (16 ± 2 beats per minute) Correlation of the con

identical The patient was instructed to breathe quietly At least two sets of recordings separated by a 10 minute interval, were obtained, each in cluded 15 cardiac cycles The intervals reported were calculated from eight consecutive cardiac cycles read to the nearest five milliseconds The average of the two sets represented the control value

To determine the degree of autonomic in fluences on STI, 28 patients from all three groups were given first propranolol (Inderal) 10 mg in travenously over a seven minute period and another two sets of recordings were obtained 10 and 15 minutes later In 10 of these patients, following intravenous propranolol, atropine sul fate (0 03 mg per kilogram of body weight) was given and a third set of recordings was obtained five minutes after the end of the atropine injec tion Arterial pressure was measured each time the systolic time intervals were recorded In seven patients with marked blood pressure fluc tuations recordings were obtained on two sepa rate occasions (more than two days apart) to study the effects of spontaneous fluctuations of arterial pressure on STI

Total electromechanical systole (Q A_2) was measured from the onset of the Q wave to the initial high frequency vibrations of the aortic component of the second heart sound (A_2) The left ventricular ejection time (LVET) was meas ured from the beginning of the rapid upstroke of the indirect carotid artery tracing to the trough of the carotid incisura The PEP was obtained by subtracting LVET from Q A_2 The isovolumic contraction period (IVCP) was determined by subtracting the Q 1 interval (from beginning of ventricular depolarization to the first high fre quency vibrations of the mitral component of the first heart sound) from PEP

LVET was corrected for heart rate according to the formula[8]

$$LVET_c (msec) = LVET + 1\ 7\ HR\ (males)$$
$$= LVET + 1\ 6\ HR\ (females)$$

PEP and IVCP do not depend to a significant extent upon the heart rate as such and no correc tion was made [6 9 10] The ratio of diastolic pressure to IVCP (DP/IVCP) was calculated, it provided an index of the mean rate of rise of left ventricular pressure during the initial phase of ventricular contraction, it was found by Landry and Good yer[11] to correlate closely with maximum dp/dt measured directly in the left ventricle

Hemodynamic studies were performed in 31 patients in the morning after an overnight fast without prior premedication In about half of these patients, STI were determined at the same time as the hemodynamic study in all the rest they were obtained the day before the study A venous catheter was inserted through an an tecubital vein to the level of the superior vena cava and an arterial catheter was inserted by a modified Seldinger technique via the brachial ar tery either to the axillary artery or to the ascend ing aorta Indocyanine green dye was injected centrally and arterial blood was withdrawn for cardiac output determination as described pre viously [3] Heart rate was obtained from a con tinuous electrocardiogram Stroke volume was calculated by dividing cardiac output by rate left ventricular ejection rate, by dividing stroke volume by ejection time (seconds) These mea surements were corrected for body surface area and expressed as cardiac stroke, and left ventric ular ejection rate indices

Statistical significance and correlation coeffi cients were calculated by standard methods [12]

Results

Systolic time intervals

Control measurements Average values for hy pertensive patients as one group were not differ ent from normal averages except for an elevated DP/IVCP ratio in the hypertensive group (Table II) Such averages however obscured significant differences between clinically well demarcated groups (Figs 1 through 4) Patients with bor derline hypertension had short PEP and IVCP (93 ± 2 1 and 28 ± 1 7 msec respectively) (mean ± S E) a small PEP/LVET ratio (0 323 ± 0 009) and a high DP/IVCP (3, 484 ± 257 mm Hg per second) On the other hand patients with fixed established hyperten sion had prolonged PEP and IVCP (126 ± 1 9 and 57 ± 2 3 msec respectively) a high PEP/LVET ratio (0 449 ± 0 016) and low DP/IVCP (1 862 ± 113) In the group of established hyperten sive subjects with a hyperkinetic heart, PEP IVCP, and PEP/LVET were all within normal, however DP/IVCP was markedly elevated (3, 651 ± 497 mm Hg per second) There was no difference in $LVET_c$ between either of the three hypertensive groups and the normal subjects

Left ventricular hypertrophy Incidence of left ventricular hypertrophy (ECG) was different in the three groups Although patients with HEH had a higher diastolic arterial pressure than patients with fixed hypertension (122 ± 7 1 vs 111 ± 4 0 mm Hg) there was only one patient with left ventricular hypertrophy in this group compared to six patients in FEH group In 29 patients with BLH there was only one with evidence of left ventricular hypertrophy

Discussion

Most studies of cardiac participation in hypertension have relied mainly on determination of cardiac output variations[1,2] the latter are however unreliable indices of changes in myocardial contractility[4] In contrast many reports have amply confirmed the excellent correlation of some systolic time intervals such as PEP and PEP/LVET ratio with more direct measures of ventricular contractility[5,10,13] Calculation of rate of left ventricular isovolumic pressure rise by an indirect method (DP/IVCP) reflected closely the maximum intraventricular dp/dt[11] Although the latter is a good index of left ventricular contractility it is also sensitive to changes in preload, afterload, and heart rate The isovolumic contraction period was also found to correlate inversely with cardiac performance[14] These noninvasive determinations were therefore a particularly useful tool for the study and follow up of a chronic disease like hypertension In addition the response of PEP to beta adrenergic blockade provided a reliable index of adrenergic influences on the myocardium[6]

As determined in this study myocardial contractility varied widely among patients with essential hypertension This variability was masked when data from all hypertensives were averaged together irrespective of type or stage of disease (Table II) In this respect our findings agree with those of Weissler Harris and Schoenfeld[9] who also did not find significant differences from normal in chronic hypertensive patients with compensated left ventricle On the other hand, separation of essential hypertensive subjects into well defined groups allowed the recognition of significant abnormalities in cardiac contractility

Myocardial contractility was increased in BLH and in hyperkinetic established hypertension (HEH) while it was depressed in fixed established hypertension (FEH) Earlier studies have shown that cardiac output was increased in borderline hypertension[1,3,15] and in some patients with the hyperkinetic heart syndrome[16] These studies however could not define precisely the role of the heart in early hypertension because of the many factors that may influence cardiac output Also not clearly defined was cardiac participation in borderline hypertensive subjects with normal or

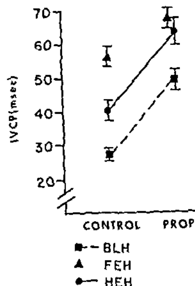


Fig 7 The prolongation of IVCP by propranolol was different among the three groups and suggested that changes in PEP were indeed related to depression in myocardial contractility The difference after propranolol might be related to level of diastolic pressure since it was not present in DP/IVCP ratio (Fig 8)

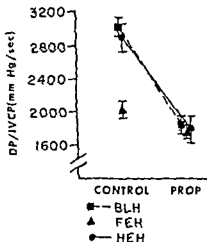


Fig 8 Changes in DP/IVCP ratio produced by propranolol in the three hypertensive groups Differences were greatly diminished following propranolol injection

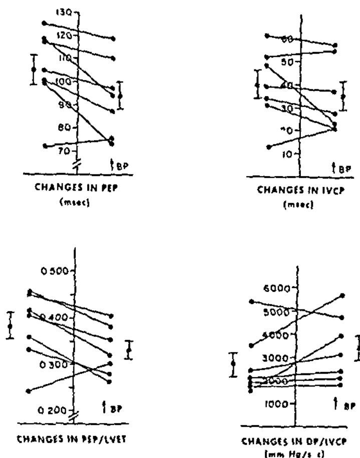


Fig 5 Recordings obtained in seven patients at a time when blood pressure was spontaneously higher than during the first study averages changed from 139/89 to 165/101 mm Hg $p < 0.001$ for difference in systolic pressure and $p < 0.01$ for difference in diastolic pressure The indices measured included PEP IVCP PEP/LVET and DP/IVCP the left hand side of each square represents values at lower blood pressure and the right column the values when pressure was elevated (see text)

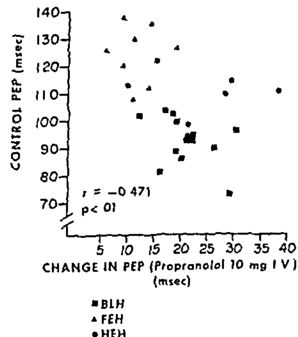


Fig 6 The prolongation of PEP by propranolol was inversely related to its duration at rest

trol cardiac rate with the degree of its slowing by propranolol was highly significant in all patients ($r = 0.672$, $p < 0.001$) PEP was prolonged by propranolol in all patients Patients with HEH and BLH showed the greatest degree of lengthening (23 ± 3 5 and 21 ± 1 4 msec, respectively) while FEH increased their PEP by 11 ± 1 4 msec only ($p < 0.005$ for HEH and $p < 0.001$ for BLH) There was an inverse relationship between the control PEP and its lengthening ($r = -0.471$ $p < 0.01$) (Fig 6) When the changes were expressed as a percentage of the control the correlation became more significant ($r = -0.709$, $p < 0.001$) After propranolol differences among the three groups diminished but were not completely abolished. Propranolol altered IVCP in the same way it affected PEP In FEH, IVCP was lengthened by 11 ± 0 2 msec, whereas in patients with BLH and HEH it was prolonged by 21 ± 1 9 and 24 ± 3 8 msec respectively (Fig 7)

As expected, propranolol reduced the mean rate of rise of left ventricular pressure (mean rate of isovolumic pressure development) in all hypertensive patients the DP/IVCP ratio was significantly decreased following beta adrenergic blockade This reduction was very impressive in BLH and HEH (1 296 ± 251 and 1,125 ± 240 mm Hg per second respectively) while less pronounced in FEH 337 ± 53 mm Hg per second (Fig 8) A highly significant linear correlation was found between control DP/IVCP ratio and its decrease by propranolol ($r = 0.937$, $p < 0.001$) (Fig 9)

Effect of atropine (Fig 10) In the 10 patients who were given atropine following propranolol there was an acceleration of cardiac rate from 63 ± 2 5 to 90 ± 3 8 beats per minute ($p < 0.001$) however, PEP changed very little from 128 1 ± 4 8 to 126 4 ± 5 4 msec The same insignificant shortening was noted in the IVCP (58 ± 3 7 to 56 ± 4 3 msec)

Hemodynamic results Significant hemodynamic differences were found among the three clinical groups Patients with BLH and HEH had cardiac output at the upper limits of normal, whereas those with FEH had a decreased cardiac output ($p < 0.001$) (Table III) All hypertensive patients had small stroke indices (normal for laboratory = 47 ± 1 04 ml /M²) FEH had the smallest stroke index and marked reduction of mean rate of left ventricular ejection ($p < 0.001$)

Table III Hemodynamic findings in hypertensive patients

	*BLH (15)**			*FEH (9)**			*HEH (7)*		
	Mean	*S E*	*p†*	*Mean*	*S E*	*p†*	*Mean*	*S E*	*p†*
CI (L/min/M²)	3 22	(0 17)	n.s.	2 38	(0 15)	<0 001	3 32	(0 26)	n.s
SI (ml/M²)	42	(2 4)	<0 025	31	(2 5)	<0 001	40	(2 9)	<0 005
MRLVE (ml/sec /M²)	151	(8 7)	n.s	116	(8)	<0 001	149	(11)	n.s

CI, cardiac index SI stroke index and MRLVE, mean rate of left ventricular ejection.
*Number of patients investigated.
†p refers to statistical significance of difference from normal values for the laboratory

significant age differences does not favor this assumption The presence of clinical and hemodynamic differences between the two groups of established hypertension suggests that they are separate entities

The mechanism of augmented cardiac contractility in our patients seemed to be an exaggerated adrenergic drive to the heart. Both borderline and hyperkinetic established hypertensive subjects had greater prolongation of PEP and IVCP following intravenous propranolol than fixed established hypertensive subjects The degree of change in PEP was inversely proportional to its duration at rest The linear and significant correlation ($r = 0\ 937$ $p < 0\ 001$) between control DP/IVCP and its reduction by propranolol added further evidence that increased cardiac contractility was directly related to beta adrenergic function The fact that restoration of cardiac rate to pre propranolol levels by atropine did not reverse the effects of propranolol on PEP and IVCP (Fig 10) indicated that changes were not rate dependent

The relationship between changes in cardiac contractility and spontaneous pressure fluctuations was studied in seven patients Rises of systemic pressure were associated with augmentation of myocardial contractility Whether this represents a cause or effect is not clear Acute animal experiments showed that IVCP was shortened by aortic hypertension this shortening was more marked whenever isoproterenol was given[11] This indicated that under conditions of increased inotropism rises of arterial pressure were associated with further augmentation of myocardial contractility Failure of propranolol therapy to prevent the fluctuation of arterial pressure in man[11] favors the assumption that increased contractility is not essential for these paroxysmal rises in pressure

In conclusion myocardial contractility seems to be increased in some patients with essential hypertension the underlying mechanism appears to be an excessive adrenergic drive Whether such a cardio adrenergic factor is a concomitant condition to the rise in systemic pressure or a basic mechanism responsible for its elevation is not yet clear As suggested by others using different methods[1 3] the alterations in systolic time intervals indicate that this factor is present at a very early stage of this disease In addition however it has become apparent that an augmented cardio adrenergic activity may persist in some patients despite the progression of hypertension and serious elevation of arterial pressure It is not yet quite clear whether persistence of an augmented adrenergic drive is beneficial or harmful to the heart in hypertension Berkson and co workers[22] have shown a greater incidence of sudden death and cardiac disease in individuals with more rapid heart rate On the other hand, left ventricular hypertrophy (ECG) was less frequent in this small group of HEH despite their very high diastolic pressure

Summary

Determination of STI in 54 untreated essential hypertensive subjects and 17 normal subjects revealed marked differences among three groups of patients Those with borderline hypertension (29) had a short PEP and IVC periods ($93 \pm 2\ 1$ and $28 \pm 0\ 7$ msec respectively $p < 0\ 001$) (mean ± S E) reduced PEP/LVET ($0\ 323 \pm 0\ 009$ $p < 0\ 05$) and increased DP/IVC ($3\ 484 \pm 257$ mm Hg per second, $p < 0\ 001$) Among those with established hypertension two groups of equal age and diastolic pressure were identified nine with marked variations in blood pressure and a hyperkinetic heart clinically and 16 with fixed hypertension none had cardiac or renal

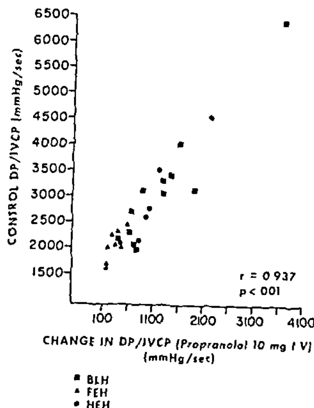


Fig 9 This figure illustrates the highly significant correlation between control DP/IVCP and its reduction by propranolol

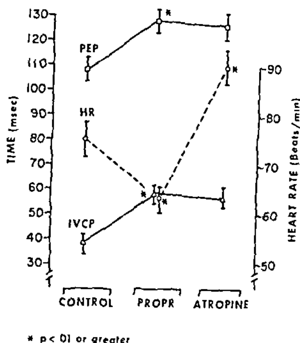


Fig 10 Acceleration of cardiac rate by atropine (0 03 mg per kilogram) did not alter either the pre ejection or isovolumic contraction period suggesting that changes produced by propranolol were not rate dependent

even reduced output [17,18] A dual approach to that problem indicated that cardiac contractility was enhanced in most patients with borderline hypertension whether cardiac output was increased or not One indication was provided by this study namely the shorter pre ejection and isovolumic contraction periods in these patients their reduced PEP/LVET ratio and increased DP/IVCP ratio (Figs 1 through 4) In another study,[17] we found a high cardiac output/cardiopulmonary volume ratio in these patients whatever their level of output in fact this high ratio was a more constant characteristic of that group than a high output Both in borderline and in established hypertension, cardiac output was correlated with cardiopulmonary volume but for any given level of the latter output was higher in the borderline hypertensive subjects This was considered as an indication of enhanced cardiac performance in these patients a conclusion similar to that afforded by the STI

Among patients with established hypertension, systolic time intervals differed markedly between the two subgroups defined clinically by the degree of pressure variability The normal' pre ejection and isovolumic contraction periods in the hyperkinetic essential hypertensive subjects (Figs 1 and 2) meant an increased rate of rise in ventricular pressure since their diastolic pressure was significantly elevated Their DP/IVCP was equal to that of borderline hypertensive subjects and the PEP/LVET was not increased as in that of patients with fixed hypertension In the latter the systolic time indices indicated that myocardial contractility was depressed in the absence of any evidence of heart failure PEP/LVET was significantly increased. The progressive nature of that depression was suggested by the findings of El Sherif, Salam and Ibrahim[19] they reported that abnormalities in systolic time intervals were more accentuated in patients with audible atrial gallop than in those without and in patients with ventricular gallop than in those with S_4 only This stepwise deterioration in contractility before frank decompensation was also documented in the studies of papillary muscles from hypertrophied hearts [20] In agreement with these findings is the higher incidence of left ventricular hypertrophy (ECG) among our patients with prolonged PEP

Why should patients with the same degree of severity of hypertension—HEH and FEH—differ in myocardial contractility is not clear The duration of hypertension might be an important factor but was difficult to estimate adequately in the majority of patients However the absence of

Experimental and laboratory reports

The electrophysiology of propranolol in man*

Stuart F Seides M D
Mark E Josephson M D
William P Batsford M D
Gerald M Weisfogel M D
Sun H Lau, M D
Anthony N Damato M D
Staten Island, N Y

Propranolol is the only beta adrenergic blocking agent currently approved for use in man Its use has been advocated for the treatment of a wide variety of cardiac rhythm disturbances [1-18] Its electrophysiologic properties have been studied in isolated tissue preparations [19-22] the intact animal [23-27] and more recently in man [28-30] The purpose of this study was to evaluate the effects of intravenous propranolol on the electrophysiologic properties of the atrioventricular conducting system in man utilizing intracardiac electrocardiography

Methods

Sixteen patients underwent right heart catheterization in the nonsedated postabsorptive state after informed consent had been obtained Patients were studied for a variety of known or suspected conduction and rhythm disorders (Table I) No patient was receiving any cardioactive agent at the time of the study A quadripolar electrode catheter was percutaneously introduced into an antecubital vein and advanced under fluoroscopic guidance to the high right atrium The distal pair of electrodes was used to stimulate the atrium and the proximal pair was used to record a high right atrial electrogram (HRA) A tripolar electrode catheter was percutaneously introduced into the right femoral vein and positioned across the tricuspid valve to obtain a His bundle electrogram (HBE) according to methods previously described.[31] In five patients an additional bipolar electrode catheter was percutaneously introduced into an antecubital vein and advanced to the apex of the right ventricle for ventricular stimulation Standard electrocardiogram (ECG) Leads I II III and V_1 and time lines (T) at 10 and 100 msec were simultaneously displayed on a multichannel oscilloscope * relayed to a tape recorder † and were later retrieved at a paper speed of 150 mm per second.*

A V nodal and His Purkinje conduction times were measured at sinus rhythm and during atrial pacing QT interval corrected to a cycle length of 1 000 msec (QTc) by the formula of Bazzett

$$(QT/\sqrt{R\ R})$$

was recorded as a measure of ventricular repolarization time [32] Sinus cycle length A V nodal and His Purkinje conduction times and QTc were measured during ten consecutive beats and averaged Refractory periods of the atrium atrioventricular node (AVN) His Purkinje system (HPS) and right ventricle were determined by the extrastimulus method[33,34] using a dual beam oscilloscope‡ and a programmed digital stimulator which delivered impulses of 1 5 msec duration at twice diastolic threshold. Each patient was paced at a constant rate to avoid the effect of changing cycle length on refractoriness

From the Ca d opulmonary Labor tory Un ted State Public Health S rvice Hosp tal, Staten I land, N Y

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R print reque ts D Anthony N D mato Cardi p lmona y Laboratory Un ted States Public Health Servic Hospital, Staten Is land, N Y 10304.

*Electron s fo Medic n White Pla ns N Y
†N rth Americ n Phill ps, Co Inc Shelton, Conn
‡Tektron x, P rtland, Ore

decompensation Those with a hyperkinetic circulation had normal PEP, IVC, and PEP/LVET despite a high diastolic pressure (122 ± 7 1 mm Hg), DP/IVC was elevated (3 651 ± 497 *mm Hg per second* p ⟨0 001) as in those with borderline hypertension In contrast, the patients with fixed hypertension had longer PEP and IVC (p ⟨ 0 001), higher PEP/LVET (p ⟨0 001) and normal DP/IVC Propranolol (10 mg intravenously) slowed heart rate and prolonged PEP and IVC more in patients with a hyperkinetic circulation and in those with borderline hypertension than in those with fixed hypertension

These results suggest the presence of an increased cardioadrenergic drive not only in borderline hypertension but also in a subgroup of patients with established hypertension Left ventricular hypertrophy (ECG) was found in 1 out of 9 patients with hyperkinetic heart but in 6 out of 16 with fixed hypertension cardiac index was high normal in the first group but reduced in the latter (3 32 vs 2 38 L/min/M² p ⟨0 001) This factor as determined by the systolic time interval might therefore, be important in determining cardiac prognosis or planning therapy

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Experimental and laboratory reports

The electrophysiology of propranolol in man*

Stuart F Seides M D
Mark E Josephson, M D
William P Batsford M D
Gerald M Weisfogel M D
Sun H. Lau, M D
Anthony N Damato M D
Staten Island, N Y

Propranolol is the only beta adrenergic blocking agent currently approved for use in man Its use has been advocated for the treatment of a wide variety of cardiac rhythm disturbances [1 18] Its electrophysiologic properties have been studied in isolated tissue preparations [19 22] the intact animal [23 27] and more recently in man [28 30] The purpose of this study was to evaluate the effects of intravenous propranolol on the electrophysiologic properties of the atrioventricular conducting system in man utilizing intracardiac electrocardiography

Methods

Sixteen patients underwent right heart catheterization in the nonsedated postabsorptive state after informed consent had been obtained Patients were studied for a variety of known or suspected conduction and rhythm disorders (Table I) No patient was receiving any cardioactive agent at the time of the study A quadripolar electrode catheter was percutaneously introduced into an antecubital vein and advanced under fluoroscopic guidance to the high right atrium The distal pair of electrodes was used to stimulate the atrium and the proximal pair was used to record a high right atrial electrogram (HRA) A tripolar electrode catheter was percutaneously introduced into the right femoral vein and positioned across the tricuspid valve to obtain a His bundle electrogram (HBE) according to methods previously described.[31] In five patients an additional bipolar electrode catheter was percutaneously introduced into an antecubital vein and advanced to the apex of the right ventricle for ventricular stimulation Standard electrocardiogram (ECG) Leads I II III and V_1 and time lines (T) at 10 and 100 msec were simultaneously displayed on a multichannel oscilloscope * relayed to a tape recorder † and were later retrieved at a paper speed of 150 mm per second *

A V nodal and His Purkinje conduction times were measured at sinus rhythm and during atrial pacing QT interval corrected to a cycle length of 1 000 msec (QTc) by the formula of Bazzett

$$(QT/\sqrt{R\ R})$$

was recorded as a measure of ventricular repolarization time [32] Sinus cycle length A V nodal and His Purkinje conduction times and QTc were measured during ten consecutive beats and averaged. Refractory periods of the atrium atrioventricular node (AVN) His Purkinje system (HPS) and right ventricle were determined by the extrastimulus method[33 34] using a dual beam oscilloscope‡ and a programmed digital stimulator which delivered impulses of 1 5 msec duration at twice diastolic threshold. Each patient was paced at a constant rate to avoid the effect of changing cycle length on refractoriness

From the Cardiopulmonary Laboratory United States Public Health Service Hospital, Staten Island, N Y

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Reprint requests Dr Anthony N Damato Cardiopulmonary Laboratory United States Public Health Service Hospital, Staten Island, N Y 10304.

*Electronics for Medicine White Plains N Y
†North American Phillips, Co Inc Shelton Conn
‡Tektronix Portland, Ore

Table I Clinical data for 16 patients

Patient No	Age	Sex	Dose of propranolol (mg)	Diagnosis
1	59	M	9	HHD VPB s
2	26	M	6	? Myocarditis VPB s
3	50	M	8	UHD RBBB
4	60	M	6	ASHD RBBB
5	71	M	8	ASHD RBBB-LAHB
6	25	F	5	PAT
7	17	F	5 5	PAT
8	43	F	6	PAT
9	60	M	6	ASHD VPB s
10	35	F	6	PAT
11	39	M	9 5	NHD ?PSVT
12	20	M	4 5	PAT
13	34	F	6	UHD ST PAT
14	68	M	7	ASHD LBBB
15	28	F	6	NHD ?PSVT
16	32	F	6 5	NHD ?PSVT

HHD = hypertensive heart disease VPB s = ventricular premature beats UHD = unknown heart disease ASHD = arteriosclerotic heart disease PSVT = paroxysmal supraventricular tachycardia NHD = no heart disease LBBB = left bundle branch block RBBB = right bundle branch block LAHB = left anterior hemiblock PAT = paroxysmal atrial tachycardia and ST = sinus tachycardia

The atrium was driven at a basic cycle length and following every eighth driven beat a premature stimulus was introduced at progressively shorter intervals up to the point of atrial refractoriness A similar procedure was used in stimulating the ventricle

After control determinations were completed each patient received 0 1 mg per kilogram of propranolol intravenously at a rate of 1 0 mg per minute (patient No 12 received a dose of only 0 05 mg per kilogram due to the appearance of significant sinus bradycardia and periods of junctional escape rhythm during the infusion) Total dose ranged from 4 5 to 9 5 mg (Table I) Electrophysiologic studies were repeated five minutes following the infusion and were completed within 45 to 60 minutes Blood pressure was carefully monitored throughout

Refractory periods were determined at one to four differing basic cycle lengths for any given patient before and after propranolol administration and these results were averaged for each patient to avoid having any individual patient disproportionately influence the data The data were analyzed using the Student's t test for paired data

Blood samples were obtained just prior to the propranolol infusion (control) and at the end of the study in fourteen patients Duplicate samples of 10 ml were drawn into heparinized tubes and the plasma was promptly separated and frozen for later analysis Plasma propranolol concentration was determined fluorometrically as described by Shand Nuckolls and Oates[35]

Definition of terms

A V nodal conduction time is defined as the A H interval measured from the onset of the low atrial electrogram to the onset of the His bundle deflection (normal values for this laboratory, 60 to 140 msec)

His Purkinje conduction time is defined as the H V interval measured from the initial deflection of the His potential to the earliest point of ventricular depolarization from either the ECG leads or the intracardiac electrogram (normal values for this laboratory, 30 to 55 msec)

Effective refractory period (ERP) of the atrium is defined as the longest $S_1 S_2$ interval at which S_2 fails to depolarize the atrium S representing the stimulus artifact

ERP of the A V node is defined as the longest $A_1 A_2$ interval at which A_2 fails to depolarize the His bundle

Functional refractory period (FRP) of the A V node is defined as the shortest $H_1 H_2$ interval that results from any $A_1 A_2$ so long as A V conduction is not limited by atrial refractoriness or, if it is, with $H_1 H_2$ intervals that had already reached a minimum and had begun to increase

ERP of the His Purkinje system is defined as the longest $H_1 H_2$ interval at which H_2 fails to conduct to the ventricles

Relative refractory period (RRP) of the His Purkinje system is defined as the longest $H_1 H_2$ interval at which H_2 conducts to the ventricles with a longer H V time than the basic drive beat or with a QRS of aberrant configuration Although it is recognized that the HPS is a trifascicular system, in the absence of multiple recording sites along individual fascicles, it is not always possible to distinguish the ERP from the RRP of any given fascicle Thus for the purposes of this study it was elected to consider the HPS as a single functioning unit

Table II Summary of results of propranolol during sinus rhythm and atrial pacing

Patient No	SCL		A H		H V		AVN W		QTc	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
1	785	870	135	155	50	50	370	430	440	429
2	560	590	75	85	45	48	300	355	448	386
3	870	900	95	110	55	55	400	430	413	390
4	810	925	90	115	42	42		370	461	459
5	1 150	1 150	115	115	35	35	460	505	332	332
6	680	745	105	105	60	60	375	380	419	419
7	620	960	90	105	40	40		315	438	378
8	*780*	*890*	*120*	*130*	*50*	*50*	500	600	408	409
9	815	850	85	90	90	90		350	427	429
10	730	880	70	90	40	40		375	458	416
11	830	910	80	85	50	50	380	380	368	368
12	950	1 255	115	125	50	50	425	600	389	343
13	540	575	80	80	60	60			450	416
14	1 060	1 145	90	105	70	70			350	360
15	660	900	130	140	50	50	350	460	419	380
16	825	1 175	85	95	40	40		330	463	387
Mean+	792	920	98	108	52	52	396	460	418	394
	p ⟨ 0 001		p ⟨ 0 001				p ⟨ 0 001		p ⟨ 0 005	

Abbr vi ti ns SCL = sinus cy le l ngth AVN W = longest pac d atrial cycl length produc ng Wenckebach A V nodal block QTc = corrected QT in terval d ring sinus rhythm = u able to induce Wenckeb ch A V nodal bl ck during atrial pacing +P ired values only (see text)

Table III Summary of results of propranolol on refractory periods

Patient No.	CL studied	Atrium ERP		A V node FRP		A V node ERP		His Purkinje system RRP		His Purkinje system ERP		Ventricular ERP	
		Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
1	2	230	235	388	422	270	290	†	†	–	–	–	–
2	1	220	230	350	370	290	300	†	†	–	–	–	–
3	3			448	472	313	357	†	†	–	–	–	–
4	3	277	283	365	400	¶	¶	#	#	†	†	255	245
5	4	248	240	482	489	364	380	#	#	†	†	235	245
6	2	180	180	380	413	¶	295	395	†	†	†	240	240
7	4	193	220	339	378	¶	¶	#	#	†	†	–	–
8	1	260	260	600	630	480	510	†	†	†	†	–	–
9	3	180	183	352	357	273	280	375	375	†	†	–	–
10	1	190	190	375	410	¶	¶	†	†	†	†	–	–
11	3	250	260	350	375	280	310	355	†	†	†	–	–
12	3	277	293	498	557	428	473	#	#	†	†	250	250
13	3	175	180	353	380	210	227	†	†	†	†	–	–
14	3	263	253	¶	¶	¶	¶	445	445	415	415	300	265
15	2	240	260	370	415	¶	340	†	†	†	†	–	–
16	3	217	217	¶	¶	¶	¶	410	410	370	370	–	–
Mean‡		227	232	404	433	323	347	410	410	393	393	256	249
		p = 0 05		p ⟨ 0 001		p ⟨ 0 001						p ⟩ 0 4	

*Tech c l difficulty with atrial wir
¶ Study lim ted du to trial refractoriness
†Study lim ted to AVN refractoriness.
#V lues ot c mparable due to inability to obtain precisely equival nt H_1H_2 nterval (see text)
‡P ired values only (see text).
Abbreviations ERP = effective refra tory period, RRP = r lative ref actory period, HPS = His Purk nje system CL = cy le le gths FRP = functional ref ctory period, and AVN = atrioventricular node

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10	35	F	6	PAT
11	39	M	9 5	NHD ?PSVT
12	20	M	4 5	PAT
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ERP of the His Purkinje system is defined as the longest $H_1 H_2$ interval at which H_2 fails to conduct to the ventricles

Relative refractory period (RRP) of the His Purkinje system is defined as the longest $H_1 H_2$ interval at which H_2 conducts to the ventricles with a longer H V time than the basic drive beat or with a QRS of aberrant configuration Although it is recognized that the HPS is a trifascicular system, in the absence of multiple recording sites along individual fascicles, it is not always possible to distinguish the ERP from the RRP of any given fascicle Thus for the purposes of this study it was elected to consider the HPS as a single functioning unit

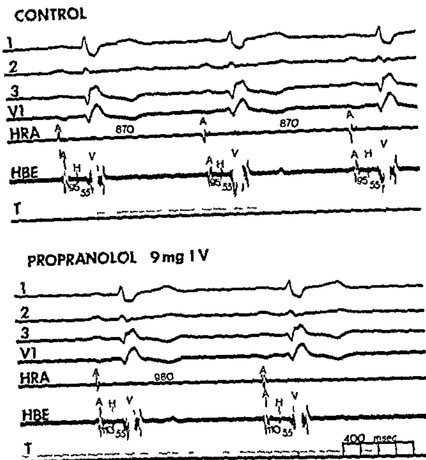


Fig 2. Effect of propranolol on sinus cycle length and QTc interval. In the upper (control) panel spontaneous sinus cycle length is 870 msec whereas after 9 mg of propranolol (lower panel) it increases to 980 msec A H interval increases from 95 msec to 110 msec H V interval remains constant at 55 msec the upper limit of normal QT interval remains constant at 385 msec but when corrected for difference in rate QTc is 25 msec shorter after propranolol

in all patients Propranolol did not affect the H V interval during sinus rhythm or at any paced atrial cycle length

QTc interval was shortened in 9 out of 16 patients and unchanged in seven with a mean net change of −24 msec ($p < 0.005$)

Fig 2 illustrates the effects of propranolol on sinus cycle length and QTc interval

ERP of the atrium was increased in 9 out of 15 patients unchanged in four patients and decreased in two patients for a net mean change of +5 msec. This reached borderline statistical significance at $p = 0.05$

FRP of the A V node was increased in all 14 patients in whom it could be measured with a net mean change of + 29 msec ($p < 0.001$)

ERP of the A V node was increased in all nine patients in whom it could be measured with a net mean change of + 24 msec ($p < 0.001$) (Fig 3)

RRP of the HPS was unchanged in all three patients in whom precisely equivalent $H_1 H_2$ intervals were obtained during the control and study periods In two additional patients (Nos 6 and 11) QRS aberration which was induced during the control period was not observed after propranolol as the lengthening of the FRP of the AVN prevented the RRP of the HPS from being reached In four additional patients the RRP of the HPS was reached both during control and study periods However in these patients propranolol induced A V nodal delay during programmed atrial stimulation prevented the occurrence of precisely equivalent $H_1 H_2$ intervals before and after the drug Hence although the values obtained for RRP in these patients were not truly comparable in no case did the point of

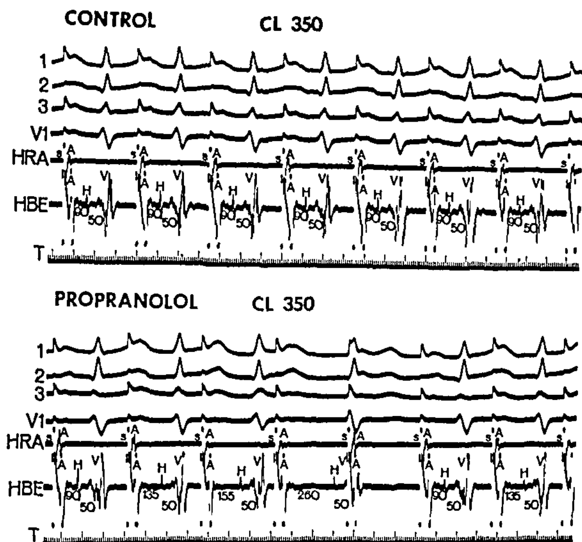


Fig 1 Effect of propranolol on A V nodal conduction during atrial pacing From top to bottom in each panel are standard Leads I II III and V_1 high atrial electrogram (HRA) His bundle electrogram (HBE) and time lines (T) at 10 and 100 msec S A H and V represent stimulus artifact atrial His bundle and ventricular deflections respectively Similar abbreviations will be used for all subsequent figures In both panels the atrium was stimulated at a cycle length of 350 msec In the upper (control) panel the A H interval is constant at 90 msec and there is 1 1 A V conduction After 6 mg of propranolol (lower panel) the A H interval progressively lengthens until the fifth atrial beat is blocked in the A V node—a pattern of Wenckebach block Note that the H V interval remains constant at 50 msec

ERP of the ventricle is defined as the longest S_1 S_2 interval at which S_2 fails to depolarize the ventricle during ventricular stimulation

Results

The results are summarized in Tables II and III Note that mean values given in these tables were calculated only from patients with paired data

Sinus cycle length was increased in 15 out of 16 patients with a mean net change of + 128 msec ($p < 0.001$) The one patient in whom there was no significant change (patient No 5) had a very long cycle length during the control period

A V nodal conduction time was increased during sinus rhythm in 13 out of 16 patients and unchanged in three patients with a mean net change of + 10 msec ($p < 0.001$) During atrial pacing at cycle lengths of 375 to 660 msec propranolol consistently increased the A H interval above control values in the same 13 patients The paced atrial cycle length at which A V nodal Wenckebach block occurred following propranolol was increased in 7 out of 9 patients (mean = + 64 msec) ($p < 0.001$) in whom this could be measured Five patients who did not manifest A V nodal Wenckebach block during the control period did so after propranolol administration (Fig 1)

His Purkinje conduction time was unchanged

pear to be an obvious correlation between the plasma level of propranolol and the magnitude of its electrophysiologic effect

There were no significant side effects and blood pressure fell less than 10 mm Hg in all cases

Discussion

Significant effects of intravenous propranolol were observed on spontaneous sinus rate A V nodal conduction ventricular repolarization and functional and effective refractory periods of the A V node In particular *no* consistent effects on the His Purkinje system were seen This is in agreement with prior studies in man[28 30 32] and recent studies in the intact dog[23] Propranolol s effect on the A V node explains its efficacy in controlling ventricular rate in atrial flutter and fibrillation as well as its efficacy in the treatment and prophylaxis of A V nodal re entrant supra ventricular tachycardia[1 5 13] On the other hand, since the initiation of re entrant tachycardias is dependent upon a critical delay in A V nodal conduction[36] it is conceivable that propranolol could potentiate the precipitation of a tachycardia in some patients However we did not observe this phenomenon in any of our patients Propranolol s apparent lack of effect on the HPS may allow its use in patients who have HPS conduction disease When compared with other parenterally administered anti arrhythmic drugs studied in this laboratory (Table V) propranolol most closely resembles digoxin[37] has effects opposite to that of atropine[38] and differs from quinidine[39] and procaine amide[40] in that these drugs decrease the refractory period of the A V node and significantly increase the refractory period of HPS and differs from diphenylhydantoin[41] and lidocaine[42] in that these drugs *decrease* the refractory period of the HPS

The mechanism of action of racemic (d l) propranolol in man has been ascribed to both its beta adrenergic blocking properties as well as its properties as a membrane stabilizing local anesthetic[1 3 12] In microelectrode studies of isolated canine Purkinje fibers[19] and rabbit atrial muscle[22] both the dextro (d) isomer of propranolol which possesses little beta blocking activity as well as the beta blocking levo (l) isomer have been shown to cause changes in the action potential similar to that seen with the quinidine like group of anti arrhythmics. These findings include decreased membrane responsiveness decrease in the maximal velocity and overshoot of phase zero decrease in the rate of spontaneous phase 4 depolarization and decreased conduction velocity In contrast to quinidine propranolol decreased the total duration of the action potential by shortening the early phase of repolarization and decreased the ERP of canine Purkinje fibers However the concentrations of propranolol used in these studies (0 3 to 10 μg per milliliter) were far in excess of those achieved clinically while in lower concentrations (100 ng per milliliter) more analogous to clinical levels and at which *no* direct effects are seen *only* (l) or racemic propranolol could block the changes in the action potential induced by epinephrine[19] Whitsett and Luc

Table IV Plasma propranolol levels (end of study)

Patient No	*Plasma propranolol (ng/mL)*
1	14
2	26
3	20
4	29
5	7
6	5 5
7	6
8	—
9	11
10	—
11	20
12	16
13	8
14	10
15	5
16	13
Mean	13 6

Table V Drug effects on refractoriness of cardiac tissues in man

Drug	*Atrium*	*A V node*	*His Purkinje system*
Propranolol	±	+	0
Digoxin	?	+	0
Atropine	±	−	0
Quinidine	+	−	+
Procaine amide	+	−	+
Diphenylhy dantoin	±	±	−
Lidocaine	±	±	−

Abbreviations + = increases − = decreases 0 = no change ± = variable effect and ? = not studied.

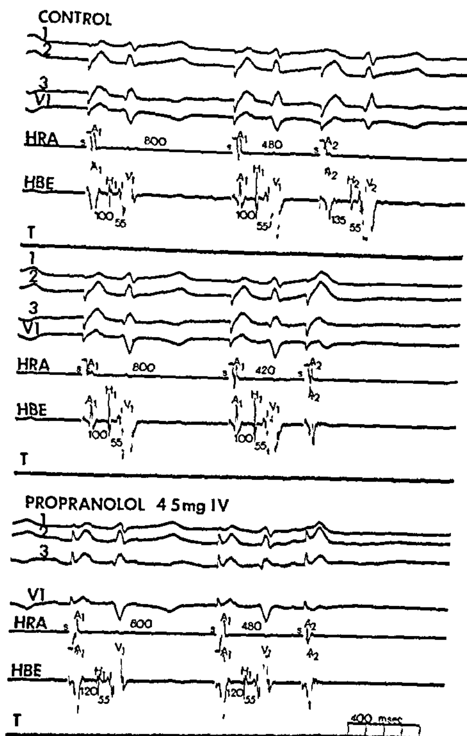


Fig 3 The effect of propranolol on the ERP of the A V node In all panels the atrial cycle length is 800 msec In the upper (control) panel a premature stimulus introduced at 480 msec results in A V conduction and ventricular depolarization In the middle (control) panel the premature stimulus is introduced at 420 msec resulting in failure of conduction above the bundle of His i e in the A V node—defining the ERP of that tissue Following 4 5 mg of propranolol (lower panel) a premature atrial depolarization introduced at 480 msec blocks in the A V node—an increase in the ERP of the A V node of 60 msec

H V prolongation or QRS aberration vary from the control value by greater than 10 msec lending further support to the concept that propranolol has little, if any, effect on the RRP of the HPS

ERP of the HPS was unchanged in two patients in whom it could be measured

ERP of the ventricle was unchanged in 2 out of 5 patients increased in two patients and decreased in one patient with a net mean change of −7 msec ($p > 0\ 4$)

Plasma propranolol levels averaged 13 6 ng per milliliter (range 5 to 29 ng per milliliter) at the end of the study (Table IV) There did not ap

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chesi[27] compared the effects of racemic and (d) propranolol on the A V *conducting system in the* intact dog in two dose ranges, 0 5 mg per kilogram and 5 0 mg per kilogram [27] *At a dose of* 0 5 mg per kilogram, only the racemic mixture depressed conduction while at the larger doses both drugs produced only a small, quantitatively similar further depression of A V conduction They concluded that beta adrenergic blockade was more important than "nonspecific mecha nisms in the clinical action of racemic pro pranolol One study in man which compared racemic with (d) propranolol showed racemic propranolol to be far more effective in decreasing sinus rate and decreasing ventricular response in atrial flutter and fibrillation, while the effects on ectopic beats were unimpressively similar for both [12]

The plasma level of propranolol at the end of our study period averaged 13 6 ng per milliliter Coltart and Shand[43] demonstrated that plasma propranolol levels in that range (10 to 20 ng per milliliter) in man increased by tenfold the dose of isoprenaline necessary to induce a given level of sinus tachycardia, and produced a 20 to 30 per cent blockade of exercise induced sinus tachy cardia Thus, the plasma levels of propranolol achieved in this study have been demonstrated to have a significant beta adrenergic blocking effect

We believe that in clinically applied doses in man beta adrenergic blockade alone probably accounts for the effects of racemic propranolol on the atrioventricular conducting system Its lack of effect on the HPS is not surprising in view of previous work that has shown the HPS to be in sensitive to adrenergic stimulation or blockade [23 28 30 44] Propranolol s mechanism of action in sup pressing ectopic activity, however, particularly that associated with digitalis toxicity is unclear and awaits further clarification

Summary

The effects of intravenous propranolol (0 1 mg per kilogram) on the electrophysiologic proper ties of the A V conducting system were studied in 16 patients using His bundle electrograms and the extrastimulus method The drug was infused at a rate of 1 mg per minute without significant side effects Sinus cycle length was slowed in 15 out of 16 patients (average, 128 msec) AVN con duction time was increased in 13 out of 16 pa tients (average, 10 msec) during sinus rhythm and in all patients during atrial pacing AVN Wenckebach block occurred at slower paced rates in 14 patients Corrected QT interval was shortened in 9 out of 16 patients (average, 24 msec) The functional and effective refractory periods (ERP) of the AVN were prolonged in 14 out of 14 patients (average 29 msec) and 9 out of 9 patients (average 24 msec.), respectively No significant changes were seen in His Purkinje system (HPS) conduction time ERP of the *atrium relative refractory period or ERP of the* HPS or ERP of the ventricle in all patients in whom these variables could be measured Mean end study blood level was 13 6 ng per milliliter Effects on the AVN explain the efficacy of pro pranolol in (1) controlling the ventricular rate in atrial fibrillation and flutter and (2) the treat ment and prophylaxis of re entrant supra ventricular tachycardias Its lack of effects on the HPS make its use relatively safe in patients with infra His conduction disturbances

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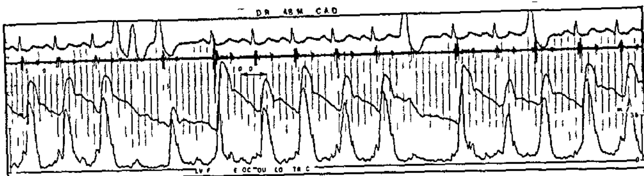


Fig 1 Simultaneously recorded Lead II (L II) of the electrocardiogram tricuspid area (TA) phonocardiogram external carotid artery pulse tracing (CT) and left ventricular outflow tract blood velocity in a 48 year-old man with coronary artery disease Ventricular premature beats reduce peak left ventricular blood flow velocity in relation to their coupling intervals The last extrasystole (QRS complex No 15) with a preceding R R interval longer than 0 5 second, produces a minimal decline of peak blood velocity The first salvo of premature depolarizations is followed by a five beat period of high low blood velocity alternans (beats Nos 7 through 11) Note that the changes in peak blood velocity are paralleled by similar variation in the amplitude of the external carotid arterial pulse tracing

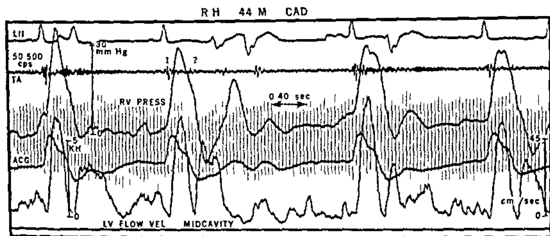


Fig 2. Simultaneously recorded Lead II (L II) of the electrocardiogram tricuspid area (TA) phonocardiogram right ventricular (RV) pressure apexcardiogram (ACG) and phasic left ventricular midcavity blood flow velocity in a 44 year-old man with coronary artery disease Catheter induced ventricular premature beats result in a shortened preceding diastolic blood flow velocity time and a decline of subsequent peak systolic and diastolic blood velocities Note that the small left ventricular systolic blood velocities are associated with minimal amplitude on the simultaneously recorded apexcardiogram

than 0 5 second, the diminution of blood velocity was most manifest Variations of peak outflow tract blood velocity were accompanied by similar alterations in the amplitude of deflection on simultaneously recorded external carotid pulse tracings Periods of postextrasystolic left ventricular blood velocity alternation were observed in four subjects (Fig 1)

Peak left ventricular midcavity systolic blood velocity declined in relation to the degree of QRS complex prematurity as described above for outflow tract records. In addition ventricular extrasystoles reduced preceding diastolic blood velocity times and effected a diminution of subsequent peak diastolic blood flow velocities The reduction of peak systolic left ventricular blood velocity induced by premature beats was paralleled by a decrease in the total deflection of the simultaneously recorded apexcardiogram (Fig 2) In two patients with aortic insufficiency peak systolic blood velocities were diminished by premature ventricular contractions yet left ven

Doppler measurement of phasic continuous left ventricular blood flow velocity during ventricular arrhythmias

Alberto Benchimol, M D
Kenneth B Desser, M D
Ting Fu Wang, M D
Phoenix Ariz.

Introduction of a Doppler flowmeter catheter into the left ventricle of man has provided new information regarding phasic, continuous and instantaneous blood flow velocity[1] We describe here the measurement of left ventricular blood velocity during selected ventricular arrhythmias in conscious human subjects

Material and method

Sixty eight patients comprised the study group There were 61 men and 7 women whose ages ranged from 22 to 70 with a mean of 46 years Fifty subjects had coronary artery disease 6 had valvular heart disease, 8 had primary myocardial or pericardial heart disease, and 4 had no evidence of cardiac abnormality Normal subjects were studied because of the presence of chest pain or systolic murmurs originally thought to represent heart disease All diagnoses were established on the basis of complete right and left heart catheterization selective coronary cineangiography and indicator dilution curves All patients were studied in the postabsorptive nonsedated state in the supine position Phasic instantaneous left ventricular blood flow velocity was measured by radiotelemetry utilizing the Doppler ultrasonic flowmeter catheter Details concerning this technique have recently been described[1] and are summarized as follows using local anesthesia with 1 per cent lidocaine the Doppler flowmeter catheter was introduced into a brachial arterial incision and passed in a retrograde fashion across the aortic valve into the left ventricle A No 7 or 8 Zucker bipolar catheter connected to a Statham P23 Db strain gauge was passed to the right heart via a medial antecubital vein cutdown for the purpose of obtaining right atrial or ventricular pressures All catheter movement was monitored by constant fluoroscopic image intensification Phasic left ventricular blood velocities, right heart pressures along with Lead II of the electrocardiogram and at times phonocardiograms apex cardiograms or external carotid pulse tracings were simultaneously recorded in an Electronics for Medicine DR 12 oscilloscopic photographic recorder Ventricular arrhythmias were either spontaneous in origin evoked by right ventricular catheter motion or in a single case, induced by performance of a Valsalva maneuver

The blood velocity waveforms described in this paper represent those recorded from left ventricular outflow tract or in a few cases the mid cavity position In the absence of aortic valvular regurgitation, outflow tract blood velocity patterns are characterized by a large systolic ejection wave followed by a smaller diastolic fraction Left ventricular midcavity wave contours are usually triphasic with atrial systolic ejection and diastolic components[1]

Results

Ventricular premature beats Left ventricular blood flow velocity was monitored during ventricular extrasystoles in 53 subjects Premature depolarizations reduced peak outflow tract blood velocities in direct relation to their coupling intervals when the latter were less

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Reprint requests Dr Alberto Benchimol Good Samaritan Hospital P O Box 2989 Phoenix Ariz 85062

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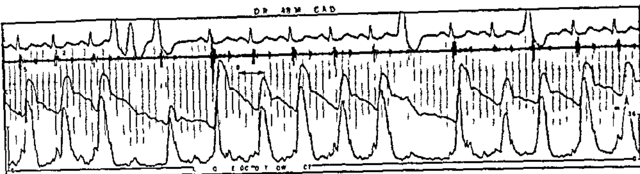


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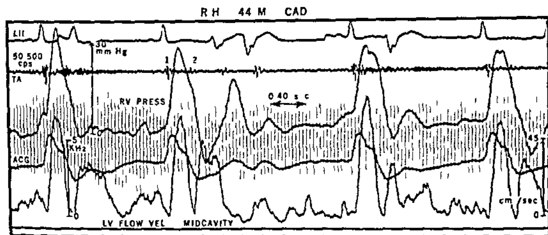


Fig 2 Simultaneously recorded Lead II (L II) of the electrocardiogram tricuspid area (TA) phonocardiogram right ventricular (RV) pressure apexcardiogram (ACG) and phasic left ventricular midcavity blood flow velocity in a 44 year old man with coronary artery disease Catheter induced ventricular premature beats result in a shortened preceding diastolic blood flow velocity time and a decline of subsequent peak systolic and diastolic blood velocities Note that the small left ventricular systolic blood velocities are associated with minimal amplitude on the simultaneously recorded apexcardiogram

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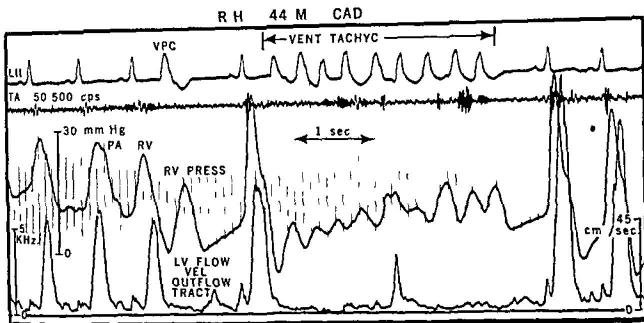


Fig 5 Simultaneously recorded Lead II (L II) of the electrocardiogram tricuspid area (TA) phonocardiogram continuous pulmonary artery (PA) and right ventricular (RV) pressures and left ventricular outflow tract blood velocity in a 44 year-old man with coronary artery disease A paroxysm of ventricular tachycardia effects a marked decline of left ventricular blood velocity and only a single small systolic flow velocity wave is recorded during the arrhythmia

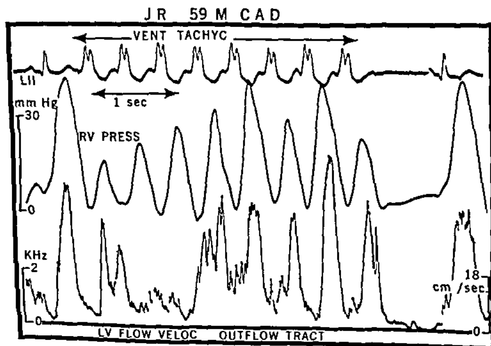


Fig 6 Simultaneously recorded Lead II (L II) of the electrocardiogram right ventricular (RV) pressure and left ventricular outflow tract blood velocity in a 59 year old man with coronary artery disease An episode of ventricular tachycardia produces an initial 80 per cent decline of peak flow velocity Subsequent left ventricular blood velocities return to control levels The alterations of phasic left ventricular blood velocity are generally paralleled by concordant changes in phasic right ventricular pressure

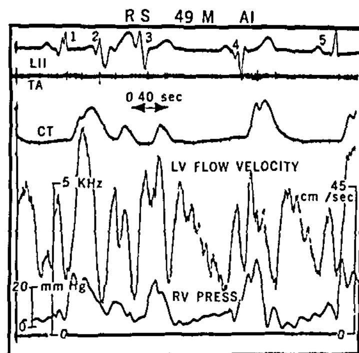


Fig 3 Simultaneously recorded Lead II (L II) of the electrocardiogram tricuspid area (TA) phonocardiogram external carotid arterial pulse tracing (CT) left ventricular outflow tract blood velocity and right ventricular (RV) pressure in a 49 year old man with aortic insufficiency Compared with sinus beat No 5 and ventricular fusion beat No 1 ventricular premature beats Nos 2 and 3 along with an escape beat (No 4) are associated with lower peak systolic blood velocities Peak diastolic blood velocity remains relatively stable throughout the record.

tricular diastolic blood velocities remained stable (Fig 3)

Ventricular tachycardia A total of 24 episodes of ventricular tachycardia were recorded in 18 subjects These tachyarrhythmias produced a 62 per cent average decline of peak left ventricular blood velocity for the study group (Fig 4) The most profound decrease of phasic blood velocity was observed in a 44 year old man with coronary artery disease In this latter subject, only one of nine QRS complexes recorded during ventricular tachycardia generated a phasic systolic blood velocity wave (Fig 5) In three patients phasic left ventricular blood velocity rapidly returned to control levels after an initial decline during ventricular tachycardia (Fig 6) A 54 year old woman with no catheterization evidence of heart disease presented with a history of syncopal like episodes during straining at stool Voluntary execution of the Valsalva maneuver produced bursts of ventricular tachycardia These tachyarrhythmias reduced peak left ventricular outflow tract blood velocity by an average of 50 per cent (Fig 7)

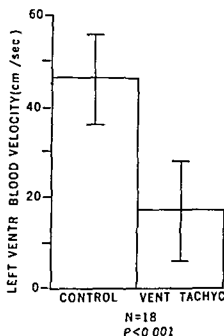


Fig 4 Mean values (± 1 standard deviation) for peak left ventricular blood velocity during control rhythm and ventricular tachycardia in 18 subjects. control = 46 ± 10 cm per second ventricular tachycardia = 17 ± 11 cm per sec ond P < 0 001

Discussion

The findings described here demonstrate the unfavorable influence of ventricular arrhythmias on phasic left ventricular blood flow velocity in conscious man Reductions of left ventricular pressure, stroke output and other indices of left ventricular performance have previously been described in human subjects during ventricular tachycardia These observations have been generally based on phasic left ventricular pressure measurement and indicator dilution curves obtained during elective ventricular pacing [2-5] Diminution of the diastolic filling time, reduced coronary blood flow and in turn less forceful left ventricular contraction produced the decline of blood cell velocity observed in the course of ventricular arrhythmias Shortened diastolic left ventricular blood velocities noted at midcavity sites indicate the adverse effects of tachyarrhythmias on left ventricular filling On the other hand maintenance of peak diastolic blood velocities in subjects with ventricular arrhythmias and aortic valvular regurgitation can be ascribed to retrograde directional blood flow from the aorta to the left ventricular cavity Enhanced reverse aortic blood velocity has been noted to occur in some patients during ventricular arrhythmias and may be secondary to imcomplete aortic

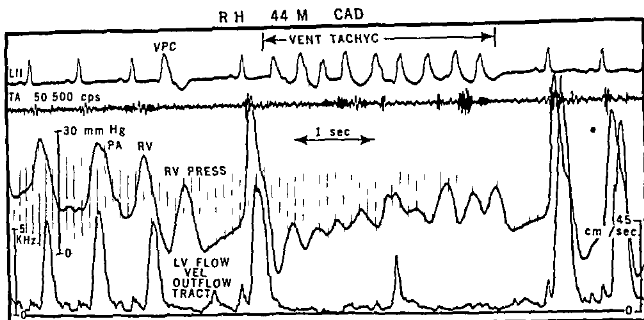


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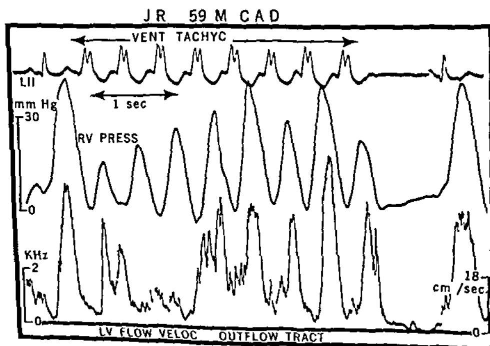


Fig 6 Simultaneously recorded Lead II (L II) of the electrocardiogram right ventricular (RV) pressure and left ventricular outflow tract blood velocity in a 59 year-old man with *coronary artery disease* An episode of ventricular tachycardia produces an initial 80 per cent decline of peak flow velocity Subsequent left ventricular blood velocities return to control levels The alterations of phasic left ventricular blood velocity are generally paralleled by concordant changes in phasic right ventricular pressure

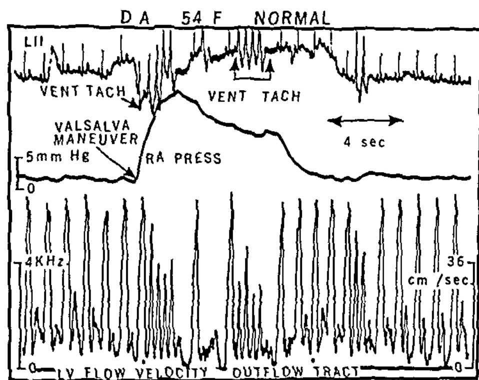


Fig 7 Simultaneously recorded Lead II (L II) of the electrocardiogram mean right atrial (RA) pressure and phasic left ventricular outflow tract blood velocity in a 54 year old woman with no catheterization evidence of heart disease Straining against a closed glottis results in a rise of mean right atrial pressure and two episodes of ventricular tachycardia The tachycardias reduce peak blood flow velocity by an average of 50 per cent

valvular closure during such rhythm disturbances[6]

Of interest was the recording of postextrasystolic left ventricular blood velocity alternation in four subjects To our knowledge this represents the first description of blood velocity alternans within the left ventricle of man Such high low alternation of peak blood velocity is probably the underlying basis for documented aortic flow alternation and may be due to beat to beat changes of end diastolic myocardial fiber length and ventricular contractility[7]

In three patients peak left ventricular blood velocities rapidly returned to near control levels after an initial decline during ventricular tachycardia This latter observation can be attributed to cardiac potentiation possibly mediated via the sympathoadrenal system[8,9] Particularly noteworthy was the marked reduction of peak left ventricular blood velocity observed in a subject with paroxysmal ventricular tachycardia during performance of a Valsalva maneuver Straining against a closed glottis has been demonstrated to result in a diminution of coronary blood velocity which is related to the degree of concomitant right atrial pressure rise[10] It is possible that the myocardium of this patient with normal coronary arteries was particularly sensitive to reduced coronary perfusion produced by straining

The limitations and advantages of Doppler catheter measurement of left ventricular blood velocity have been previously described in detail[1] Despite the fact that the crystal tipped catheter senses the velocity of blood cells in a chamber with rapidly changing dimensions this technique is currently the only method which can instantaneously measure phasic left ventricular blood velocities on a continuous basis Previous studies have demonstrated the untoward influence of ventricular tachycardia on aortic[11] along with coronary[12] carotid[13] renal[14] superior mesenteric[15] and peripheral arterial blood velocities[16] It is apparent that the decline of flow velocities in these regional circulations can be linked to the basic left ventricular abnormalities noted in this study

Summary

Phasic instantaneous left ventricular blood velocity was continuously measured by means of the Doppler ultrasonic flowmeter catheter radiotelemetry system in 68 patients with ventricular arrhythmias Ventricular premature

depolarizations reduced peak left ventricular blood velocities in relation to their respective coupling intervals with R R intervals less than 0 5 second producing the greatest decline Ventricular tachycardia in 18 subjects produced a 62 per cent mean decrease in left ventricular blood velocity In a single subject performance of the Valsalva maneuver effected ventricular tachycardia and a concomitant marked diminution of phasic left ventricular blood velocity These findings demonstrate the untoward influence of ventricular extrasystoles and tachycardia on left ventricular blood velocity and provide the underlying basis for reductions of blood velocity previously demonstrated in the regional circulations of man during similar arrhythmias

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Experimental coronary artery ligation in conscious dogs six months after bilateral cardiac sympathectomy

Ronald A F Fowlis M B, F R C P (C)
Christopher T M Sang M B, M R C P F R C S
Paul M Lundy, M Sc
Suraj P Ahuja, M B B S, F R C P (C), F A C C
Howard Colhoun Ph D
London Ontario Canada

The role of the sympathetic nervous system and myocardial catecholamines in inducing ventricular arrhythmias and fibrillation (VF) following acute myocardial infarction has been studied in dogs for many years In one study,[1] bilateral stellate ganglionectomy and sympathectomy (BSTG) carried out 28 days earlier reduced the 24 hour mortality after left circumflex coronary artery (LCA) occlusion from 80 per cent to 0 per cent in conscious dogs Other studies[2-8] with one exception[9] showed similar, though less impressive, results

There are several factors influencing mortality and arrhythmias which vary in the above experiments and which may account for different results, these being ligation of the coronary artery the site of the ligature, the method of occlusion [8] the use of anesthetic agents and the interval between BSTG and coronary artery occlusion [1, 7] In conscious dogs ligation of the LCA has yielded a 75 per cent mortality as compared to 40 per cent mortality following ligation of the left anterior descending coronary artery (LAD) [2] The mortality is highest when the ligature is within 2 mm of the origin of the LCA and there are no arterial branches proximal to the ligature [1, 10] The use of anesthetic agents during occlusion alters cardiovascular autonomic regulation and hemodynamics and protects against fatal arrhythmias [2, 11, 12] The antiarrhythmic effect of BSTG has been shown to be present from 24 hours to 3 weeks when myocardial catecholamines are depleted [7, 8] However after BSTG, myocardial catecholamines return to normal levels at 5 to 16 weeks and do not correlate with functional cardiac responses to electrical sympathetic stimulation [13, 14] The role of myocardial catecholamines may be less important than the effect of circulating epinephrine released from the adrenal medulla in response to coronary ligation Circulating epinephrine increased 1 to 30 minutes after coronary ligation and high levels correlated with the frequency of cardiac arrhythmias [15, 16] Conversely, ventricular arrhythmias occurred in dogs which had been treated with reserpine and propranolol prior to coronary occlusion Functional separation of the sympathetic innervation of the heart from the central nervous system was very effective up to 19 days after BSTG, but has not been assessed by functional and histologic studies after six months [14] Cardiac sympathetic re innervation has been demonstrated 11 weeks after cardiac autotransplantation [14]

The purpose of this series of experiments was to compare a group of dogs which had BSTG performed six months previously (BSTG 6 mo) to a group of control animals with respect to mortality changes in postocclusion heart rate arrhythmias myocardial norepinephrine and the size of the myocardial infarction Functional re innervation and histologic regeneration were assessed by spinal cord stimulation and from biopsies respectively

From the Cardiac Investigation Unit, University Hospital and Department of Pharmacology University of Western Ontario London Ontario Canada

Supported by a grant from the Ontario Heart Foundation

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Reprint requests Dr Suraj P Ahuja University Hospital 339 Windermere Rd London Ontario N6G 2K3 Canada

Material and methods

Cardiac sympathectomy Twenty three adult mongrel dogs (10 to 20 kilograms) were anesthetized with intravenous Nembutal (30 mg per kilogram) and artificially ventilated Through a third interspace thoracotomy the stellate ganglion sympathetic chain with rami communicantes and ansa subclavia were exposed and electrically stimulated (5 v 30 Hz) and changes in cardiac rate were recorded. The sympathetic chain between the fifth and sixth interspaces rami from the first to fifth interspaces and ansa were divided leaving the stellate ganglion attached to two or three cervical branches Electrical stimulation of the stellate ganglion at this stage caused no increase in cardiac rate in any of the experiments The stellate ganglion and chain were excised next The ansa was explored to its junction with the vagus nerve at the lower cervical ganglion which is usually closely applied to the vagus [20] The ansa was excised at this junction where possible with the lower cervical ganglion The procedure was repeated on the opposite side two to four weeks later (mean 25 days)

Experimental coronary occlusion. Six months after BSTG (mean 190 days) the LCA was exposed at its origin from the left main coronary artery through a fourth left interspace thoracotomy under Nembutal anesthesia A loose silk ligature was applied to the LCA at the bifurcation of the left main stem coronary artery proximal to any branches arising from LCA In 16 animals the left atrial appendage was amputated for norepinephrine assay The ends of the silk ligature were exteriorized at the ventral aspect of the fourth interspace and the dorsal aspect of the fifth interspace and buried subcutaneously This procedure was performed alternately on 23 BSTG 6 mo dogs and 23 control dogs Two or three days later (mean 2 4 days) with the dogs conscious the presence or absence of sinus arrhythmia was recorded. The ends of the ligature were pulled and tied externally the electrocardiogram (Lead I) being recorded on paper for 15 minutes and on tape (Phillips ana log 7) for two hours Surviving dogs were returned to their kennels and observed frequently The rhythm strip and tape were reviewed and the arrhythmias analyzed and quantitated.

Pathologic data All dogs were autopsied soon after death or when killed with intravenous Pentothal after 48 hours The site of the ligature the occlusive nature of the ligature and the size of myocardial infarction when grossly present were observed. The scar tissue in the region of the excised stellate ganglion was dissected with pleura and muscle fixed in 10 per cent buffered formalin and prepared with Bodian's impregnation for histologic evidence of neural regeneration

Table I Postocclusion mortality

Period after occlusion	*23 BSTG 6 mo. dogs*		*23 control dogs*		*Statistical analysis chi square*
	(%)	*No*	*(%)*	*No.*	
15 min	22	5	52	12	p < 0 05
2 hrs.	35	8	52	12	NS
24 hrs.	44	10	65	15	NS
48 hrs.	52	12	65	15	NS

Min minutes, hr hours NS not significant. BSTG 6 mo bilateral stellate ganglionectomy and thoracic sympathectomy of 6 months duration all dogs which died in less than two hours developed VF except one BSTG 6 mo dog which died in asystole at one hour and 10 minutes.

Norepinephrine assay Full thickness biopsies from the healthy and infarcted segments of the left ventricle were always taken from similar sites along the LAD and LCA distribution The tissue was immediately placed in ice cold acidified (HCl) butanol After weighing it was finely divided with scissors then homogenized for six minutes with the high speed attachment of a Sorvall Omni mixer The method of Chang[21] was used for extraction of norepinephrine from the homogenate An Aminco Bowman spectrophotofluorometer was used to assay the level of norepinephrine The excitation wavelength was 385 mμ and fluorescence was measured at 485 mμ (uncorrected)

Spinal cord stimulation It proved technically difficult to assess functional responses to electrical stimulation in BSTG 6 mo dogs Initially the scar tissue in the location of the excised stellate ganglion was stimulated but due to adhesions accurate placement of the electrode was not possible In five BSTG 6 mo dogs who had survived LCA occlusion spinal cord stimulation (SCS) was carried out prior to death Under Nembutal anesthesia a lower cervical laminectomy was performed and the dura opened to expose the lower cervical and upper thoracic spinal cord and roots A stimulus (5 v 30 Hz.) was applied to the

Table II Mean percentage increase in heart rate one minute after coronary occlusion

	BSTG 6 mo			*Control*	
	No.	*Increase in HR*		*No.*	*Increase in HR*
All *dogs*	23	10 5 ± 4 5	p < 0 005	23	31 ± 4 3
Dogs which succumbed < 15 min		group A			group B
	5	20 8 ± 14 7	NS (p < 0 5)	12	35 4 ± 7 0
		NS (p < 0 5)			NS (p < 0 4)
Dogs which survived > 48 hr		group C			group D
	11	8 1 ± 5 6	p < 0 05	8	26 7 ± 5 6

NS not significant. *HR,* mean percentage increase in heart rate one minute postocclusion ± standard error of the mean No number in group. p, derived by students t test. min. minutes hr hours BSTG 6 mo bilateral stellate ganglionectomy and thoracic sympathectomy of six months duration *Groups A B C* and *D* see text.

lateral aspect of the cord at different levels and changes in cardiac rate were recorded The dogs were killed with intravenous Pentothal and the exact location of the spinal roots was confirmed at autopsy As well as the five BSTG 6 mo dogs and five control dogs, (these 10 dogs having survived LCA occlusion > 48 hours) SCS was performed on three dogs which had BSTG carried out four weeks previously (BSTG 4 wk) to assess the short term effect of BSTG on SCS and myocardial norepinephrine

All BSTG 6 mo and BSTG 4 wk animals were shown to have adequacy of cardiac sympathetic denervation by electrical stimulation of the stellate ganglion at the time of the BSTG All BSTG 6 mo and control dogs had satisfactory location of the ligature (i e proximal to any branches) and complete occlusion of the LCA

Results

Both groups of dogs (BSTG 6 mo and control animals) were similar in male/female ratio and weight. No animals showed objective signs of myocardial pain Transient restraint was frequently necessary for five to 15 seconds during pulling of the ligature presumably due to pain from the chest wall incision or pleural irritation No subsequent restraint was required

Mortality Results of postocclusion mortality in BSTG 6 mo dogs and control dogs at 15 minutes 2 hours 24 hours and 48 hours are given in Table I A significant difference ($p < 0.05$) was observed in the mortality between the two groups 15 minutes after coronary artery ligation Analysis of the dogs which succumbed during the 48 hour period of observation showed that 80 per cent of the control animals and 42 per cent of the BSTG 6 mo animals developed VF in less than 15 minutes after coronary occlusion

Arrhythmias Sinus arrhythmia (SA) was present before coronary occlusion in 23 per cent (five) BSTG 6 mo dogs and 82 per cent (18) control dogs Its presence in BSTG 6 mo animals was associated with a high mortality, i e , 60 per cent at 15 minutes and 100 per cent at 24 hours. In BSTG 6 mo dogs without SA the mortality was 11 per cent at 15 minutes and 28 per cent at 24 hours Mortality in control dogs with SA was 50 per cent at 15 minutes and 72 per cent at 24 hours

The cardiac rate one minute after coronary occlusion (Table II) showed a mean percentage increase of 10 5 ± 4 5 S E M over the pre occlusion rate in the 23 BSTG 6 mo dogs 100 ± 4 to 110 ± 3 9, and a mean percentage increase of 31 ± 4 3 S E M in 23 control dogs, 106 ± 3 5 to 138 ± 6 0 ($p < 0.005$) All animals were in sinus rhythm To determine if mortality correlated with the mean percentage increase in the postocclusion heart rate the BSTG 6 mo and control dogs were grouped into animals which succumbed in less than 15 minutes and those which survived longer than 48 hours (Groups A B C and D, respectively, in Table II) Comparison of Groups A and C with B and D confirmed that the BSTG 6 mo dogs had a lesser percentage increase in postocclusion heart rate than control dogs Comparison of Groups A and B with C and D showed that although animals which succumbed in less than 15 minutes had a greater percentage increase in postocclusion heart rate than those surviving longer than 48 hours these differences were not statistically significant. Slowing of the cardiac rate one minute after LCA ligation oc

Table III Analysis of postocclusion ventricular arrhythmias during two hours of continuous monitoring

Interval	*Mean number of VPB per minute ± S.E.M and No. of dogs in parentheses*			*Mean number of VT per minute ± S.E.M. and No of dogs in parentheses*		
	BSTG 6 mo		Control	BSTG 6 mo		Control
0 5 min.	8 2 ± 1 6 (21)	NS	5 0 ± 1 6 (21)	1 21 ± 0 27 (21)	NS	1 65 ± 0 .6 (21)
5 10 min.	3 6 ± 1 8 (17)	NS	3.3 ± 1 6 (13)	0 01 ± 0 01 (17)	NS	0 62 ± 0 45 (13)
10 15 min	4 0 ± 1 5 (17)	NS	7 6 ± 1 9 (12)	0 14 ± 0 12 (17)	NS	0 47 ± 0 27 (12)
15 60 min.	1 7 ± 0 5 (16)	NS	2 7 ± 2 0 (10)	†		†
60 120 min	1 2 ± 0 9 (15)	NS	4 7 ± 3 4 (10)	†		†

BSTG-6 mo bil teral stell te ganglionectomy nd tho acic symp thectomy of six months duration S.E.M standard error of the mean VPB ventricular prem ture beat. NS not significant m n. m nutes VT ventricular tachycardia (three or more consecutive VPB s) the magnetic tape on four dogs (tw in each group) w s inadvertently rased. † VT after 15 minutes was very uncommon in both groups

Table IV Mean values of incidence duration and onset of various arrhythmias after coronary ligation

	*BSTG 6 mo**		*Control**
Mean number of VPB per minute of dog survival during two hours monitoring	2 63 ± 0 51 (21)	p < 0 4	4 15 ± 1 33 (21)
Mean number of VT per minute of dog survival during 15 minutes postocclusion	0 72 ± 0.23 (21)	p < 0 3	1 27 ± 0 38 (21)
Mean onset of ventricular arrhythmias in first five minutes†	2 min. 12 sec ± 8 9 sec (21)	p < 0 3	1 min. 49 sec ± 14 8 sec (18)
Mean onset of terminal arrhythmia in dogs which succumbed < five min.†	2 min ± 5 sec (4)	p < 0 02	1 min. 14 sec ± 13 sec (8)
Mean duration of VT per dog in first five minutes postocclusion	5 4 ± 1 1 sec. (18)	p < 0 1	24 7 ± 13 4 sec (12)
Frequency of third degree A V block	22% (5)	‡	4% (1)

m n minutes sec seconds p derived by s udents t test mean values ± standard error of the mean with number of dogs in parentheses † time intervals are measured from moment of coronary occlus on to onset of respect e arrhythmia ‡numbers to small for Chi square

curred in only one control dog which developed VF in less than 15 minutes The cardiac rate in eight BSTG 6 mo dogs slowed from a mean pre occlusion rate of 104 ± 6.8 S E M to a mean one minute postocclusion rate of 95 3 ± 5 The out come in th se eight animals was similar to the BSTG 6 mo dogs as a whole one dog developed VF in less than 15 minutes one dog died in asys tole at 1 hour and 10 minutes, two dogs died be tween 2 and 48 hours and four dogs survived longer than 48 hours

Analysis of ventricular arrhythmias and third degree atrioventricular block is summarized in Tables III and IV All 46 dogs had ventricular ar rhythmias during the two hour period of con tinuous monitoring after LCA ligation Further more all dogs had one or more bouts of R on T phenomenon i e interruption of the T wave of the preceding cardiac cycle by an ectopic ventric ular QRS complex Statistical analysis of these arrhythmias proved difficult because of the wide range of ventricular premature beats (VPB) and

Table V Comparison of mortality with the incidence of ventricular arrhythmias

	Animals dying < 15 min	Animals surviving > 48 hours	p (t test)
BSTG 6mo. dogs			
VPB	4 6 ± 1 5 group A	2 1 ± 0 5 group C	NS p < 0 3
No	4	11	
VT†	2 0 ± 1 0	0 5 ± 0 1	NS p < 0 2
Control dogs			
VPB*	4 3 ± 1 3 group B	4 6 ± 3 2 group D	NS
No	11	8	
VT†	1 8 ± 0 6	0 3 ± 0 1	p < 0 05

BSTG 6 mo bilateral stellate ganglionectomy and thoracic sympathectomy of six months duration. No number of dogs NS not significant. ventricular premature beats measured as mean per minute of dog survival during two hours monitoring ± standard error of the mean † ventricular tachycardia measured as mean per minute of dog survival during 15 minutes postocclusion ± standard error of the mean Groups A B C and D see text

ventricular tachycardia (VT) per minute of dog survival Overall VPB and VT were less frequent in BSTG 6 mo animals The onset of ventricular arrhythmias was later, and the duration of VT was markedly shorter in BSTG 6 mo dogs compared to control dogs Also, the onset of the terminal arrhythmia in animals which succumbed in less than five minutes was significantly later in BSTG 6 mo dogs (p < 0 02)

A comparison of mortality with ventricular arrhythmias is given in Table V These arrhythmias were generally more frequent in BSTG 6 mo and control dogs which succumbed in less than 15 minutes (Groups A and B) than in animals surviving longer than 48 hours (Groups C and D) The difference in the frequency of VT between control Groups B and D was significant (p < 0 05) The incidence of ventricular arrhythmias in the eight BSTG 6 mo dogs which showed slowing of the cardiac rate one minute postocclusion was 2 2 ± 0 8 VPB per minute per dog and 0 8 ± 0 5 VT per minute per dog These results are comparable with the total BSTG 6 mo dogs (Table IV)

There was no set pattern of ventricular arrhythmias or coupling intervals in control dogs differentiating those which died in less than 15 minutes from those surviving longer than 48 hours Progressive shortening of the coupling interval (i e , the time interval between a sinus beat and the following ventricular ectopic beat) during the first few ventricular arrhythmias was seen in eight out of 11 control dogs developing ventricular fibrillation in less than 15 minutes The mean coupling interval decreased from 0 27 seconds ± 0 05 S D to 0 19 seconds ± 0 001 The mean QT interval in this group was 0 21 seconds ± 0 03 However, a similar change was found in six out of eight control dogs surviving longer than 48 hours, the mean coupling interval decreasing from 0 28 seconds ± 0 05 to 0 22 seconds ± 0 07 The mean QT interval in this group was 0 24 seconds ± 0 06 Comparable results were found in the coupling intervals of BSTG 6 mo dogs

Premonitory signs of ventricular fibrillation were an episode of ventricular tachycardia longer than 1 2 seconds or consecutive episodes of increasing durations of ventricular tachycardia The onset of the terminal arrhythmia was a typical ventricular tachycardia which persisted for several seconds before the monitor pattern changed to the characteristic pattern of VF One control dog abruptly developed ventricular tachycardia followed by VF, but most animals had several ventricular premature beats and bouts of ventricular tachycardia before the terminal arrhythmia No dogs developed the electrocardiographic pattern of VF without preceding ventricular tachycardia The ventricular premature beats invariably had a uniform electrocardiographic configuration The ventricular premature beats which occurred between 30 minutes and two hours postocclusion usually had a longer coupling interval rarely showed R on T' phenomenon, and were often interpolated Four control dogs and one BSTG 6 mo dog had short episodes of ventricular tachycardia between 60 minutes and two hours but no animals developed VF in this interval It was not known whether the three control dogs (13 per cent) and the seven BSTG 6 mo animals (30 per cent) which succumbed between two and 48 hours developed asystole or VF since the cardiac rhythm was not monitored continuously after two hours of coronary ligation

Third degree A V block developed in 22 per cent (five) BSTG 6 mo dogs and only 4 per cent (one) control dog and was associated with a high mortality in both groups

Myocardial norepinephrine The values for the

Table VI Myocardial norepinephrine*

	BSTG-4 wk.		*BSTG-6 mo*		*Control*
Left atrium mean			0 89 ± 0 28 (9)	NS	1 0 ± 0 4 (7)
Nonischemic ventricle Mean	0 13 ± 0 08 (3)	p < 0 005	0 66 ± 0 3 (11)	NS	0 68 ± 0 4 (15)
< 15 min.			0 75 ± 0 33 (4)	NS	0 86 ± 0 5 (6)
			NS p < 0 4		NS p < 0 3
> 48 hr			0 51 ± 0 25 (5)	NS	0 59 ± 0 33 (8)
Infarcted ventricle Mean			0 59 ± 0 38 (7)		0 58 ± 0 5 (10)
< 15 min.			0 69 ± 0 37 (4)	NS	0 94 ± 0 63 (4)
			NS p < 0 4		NS p < 0 1
>48 hr			0 21 ± 0 06 (2)	NS	0 3 ± 0 23 (5)

BSTG bilateral stellate g ngl nectomy and thoracic sympathectomy 4 wk four weeks d ration. 6 mo six m nths durat on < 15 ar im als dying in less than 15 minutes > 48 animals surviving longer than 48 hours NS not statistically s gnificant. p derived by students t test. Val s in mi rograms per gram f myocardium (w t w ght) ± standard deviat on with number of dogs in each group in parentheses.

Table VII Spinal cord stimulation

Group and No of dogs	*Mean resting heart rate**	*Mean heart rate after SCS†*	*Mean percentage increase*
BSTG-6 mo (5 dogs)			
1	123 ± 4	127 ± 4	3 3
2	132 5 ± 2 5	137 ± 2 5	3 8
3	80 ± 6	97 5 ± 7 5	21 9
4	102 ± 10	125 ± 5	22 5
5	91 ± 9	152 ± 2 5	67 6
Mean	105 6 ± 6 8	128 0 ± 6 2	20 8 ± 7 9 p < 0 001
Control (5 dogs) Mean	130 5 ± 5 7	218 4 ± 7 9	77 9 ± 7 3 p < 0 001
BSTG 4 wk. (3 dogs) Mean	113 6 ± 8 2	123 8 ± 10 5	10 2 ± 8 0

p values deriv d by Stud nt t test. * in beats pe minute ± stand rd erro of th me n † SCS spinal co d stimul tion (5 V 30 Hz.) M an values from stimulati n of right and left sides at lev l of s cond th ra c pin l root The increas e n heart rate when pre ent, was usually greater on the right s d than on the left d

myocardial norepinephrine (MN) content in myocardial tissue are shown in Table VI A significant reduction of MN was obtained for the three BSTG 4 wk animals Comparable MN levels were found between BSTG 6 mo and control dogs in biopsies from left atrium non ischemic ventricle and infarcted ventricle When MN levels were compared with mortality i e. when the BSTG 6 mo and control dogs were subgrouped into those dying in less than 15 minutes and those surviving longer than 48 hours higher MN values were found in the nonischemic ventricle of dogs dying in less than 15 minutes to those surviving longer than 48 hours This difference was seen in both BSTG 6 mo and control dogs but was not significant probably due to the small numbers in the subgroups The MN levels in the infarcted ventricle were not depleted abruptly after coronary occlusion but fell gradually by about 70 per cent over 48 hours in both BSTG 6 mo and control dogs No correlation was found between MN levels and the presence of sinus arrhythmia changes in postocclusion heart rate or ventricular arrhythmias

Table VIII Twenty four hour postocclusion mortality in various studies

Author	*BSTG (%)*	*Control (%)*	*Interval between BSTG and occlusion*	*Artery*	*Anesthetic*
Skelton et al[1]	14	80	7 days	LCA	None
Skelton et al[1]	0	80	28 days	LCA	None
Manning et al[2]	10	75	24 hours	LCA	None
Milch et al[3]	39	62	7 days	LAD	Nembutal
Schauer et al[4]	16	37	Immediate	LAD	Nembutal
Yodice[9]	63	73	11 25 days	LAD	Ether
Ebert et al[7]	40	52	3 weeks	LAD	Pentothal

BSTG bilateral stellate ganglionectomy and thoracic sympathectomy occ coronary occlusion, LCA left circumflex coronary artery LAD left anterior descending coronary artery

Spinal cord stimulation The results of spinal cord stimulation (SCS) at the second thoracic spinal root are shown in Table VII The three BSTG 4 wk animals showed a mean increase in cardiac rate of 10 2 per cent and the five control dogs showed a mean increase of 77 9 per cent ($p < 0\ 001$) The five BSTG 6 mo animals all of which had survived coronary artery ligation, showed variable responses to SCS Two dogs had negligi ble responses, two dogs had mild responses and only one dog had a response comparable to the control dogs Overall the BSTG 6 mo animals had a mean increase in heart rate of 20 8 per cent a value significantly different from control results ($p < 0\ 001$)

Pathologic data Histologic studies with Bodian s impregnation were performed on eight sections of scar tissue from the right and left pleura in the area of the excised stellate ganglion and sympathetic trunk in four BSTG 6 mo dogs Disorganized regenerating nerve filaments were demonstrated in only one section which was from the right side In this animal the following results were obtained sinus arrhythmia before LCA ligation, a 50 per cent increase in the one minute postocclusion heart rate high MN levels (1 12 μg per gram) and it had two VPB, with progressive shortening of the coupling interval before it succumbed from ventricular fibrillation three minutes and 30 seconds after LCA occlusion Of the three dogs with no histologic neural regeneration one died at three minutes one at 30 minutes, and one survived longer than 48 hours Their mean increase in postocclusion heart rate was 22 per cent and mean MN was 0 67 μg per gram ± 0 16 S D

The size of the myocardial infarction, when examined grossly, was comparable in both groups The pathologic changes were clearly evident at 48 hours with transmural infarction of about 50 per cent of the left ventricle The infarction involved the posterior 1/3 of the septum, the posterior and lateral walls including the posterior papillary muscle and often extended into the anterior papillary muscle Circumferentially, 70 per cent of the myocardium at the base 50 per cent at midventricular level and 30 per cent near the apex was infarcted The left atrium often showed hemorrhagic infarction as well

Discussion

The results of bilateral cardiac sympathectomy on the 24 hour postcoronary occlusion mortality carried out by a number of investigators are shown in Table VIII Differences in experimental methods make these studies difficult to compare Nevertheless all the results show that the sympathectomized dogs had a lower mortality than did control animals Recently, in experiments technically similar to ours, Khan, Hamilton and Manning[18] demonstrated a protective effect of beta adrenergic blockade in reducing ventricular fibrillation following coronary occlusion The reasons for the protective effect of sympathectomy are not known Removal of sympathetic pathways may result in the following depletion or impaired release of myocardial norepinephrine[7, 13] a diminished stimulus to the release of circulating epinephrine from the adrenal medulla[15, 16] interruption of a cardiocardiac excitatory spinal reflex[22, 23] or a combination of these mechanisms

In the present study in which no anesthetic was used during coronary ligation and only tran

sient restraint was maintained after coronary occlusion there was a significant difference in the early (< 15 minutes) postocclusion mortality i e 22 per cent in BSTG 6 mo dogs and 52 per cent in control dogs ($p < 0.05$) It was observed that 80 per cent of control animals and 42 per cent of BSTG 6 mo dogs which succumbed during the 48 hours of observation developed ventricular fibrillation in the initial 15 minutes This was the most critical period after coronary ligation and was the interval when BSTG conferred its greatest protection The protective effect was still evident at 24 hours when the mortality was 44 per cent in BSTG 6 mo and 65 per cent in control dogs Thus 44 per cent mortality in BSTG 6 mo dogs was higher than the results of Skelton and co workers[1] and McEachern Manning and Hall[2] whose methods were similar to our own except that the time between BSTG and coronary occlusion was considerably shorter in their experiments (see Table VIII) This suggests that both the degree and duration of the protective effect of BSTG decreases with increasing time interval between BSTG and coronary ligation

The presence of sinus arrhythmia in only 22 per cent (five) BSTG 6 mo dogs compared to 80 per cent in control dogs infers that sinus arrhythmia is partly mediated by the sympathetic nervous system which might have regenerated in those five BSTG 6 mo dogs which succumbed. This was supported by the high mortality (100 per cent at 24 hours) in those five BSTG 6 mo animals The BSTG 6 mo dogs had a significantly lower percentage increase in the one minute postocclusion sinus heart rate than did the control dogs ($p < 0.005$) This result suggests that the BSTG 6 mo dogs had either lower levels of circulating epinephrine or impaired release of myocardial norepinephrine or interruption of a cardiocardiac excitatory spinal reflex[22, 23] As all dogs were conscious, the variable effect of an anesthetic was eliminated It was also observed that the animals which succumbed in less than 15 minutes had a greater increase in the postocclusion heart rate than those surviving longer than 48 hours although this was statistically not significant Nevertheless, it is conceivable that the marginally greater increase in sinus heart rate may have predisposed to VF Slowing of the cardiac rate was more common in BSTG 6 mo dogs, but did not predispose to ventricular arrhythmias or VF

Analysis of the incidence of ventricular premature beats and VF confirmed the report by Harris Estandia and Tillotson[8] that in the two hours following coronary ligation these arrhythmias were less frequent in BSTG dogs than in control dogs though the differences were not significant The animals which succumbed in less than 15 minutes tended to have more frequent ventricular tachycardia than dogs surviving longer than 48 hours The duration of ventricular tachycardia was markedly shorter in BSTG 6 mo dogs The onset of ventricular arrhythmias was later in BSTG 6 mo dogs especially the onset of the terminal arrhythmia in the groups which succumbed in less than five minutes ($p < 0.02$) Thus cardiac sympathectomy even after six months reduced ventricular arrhythmias following coronary ligation Analysis of coupling intervals was not helpful in predicting which animals would develop VF The incidence of third degree A V block was higher in BSTG 6 mo dogs and was associated with a high mortality a finding noted by Khan Hamilton and Manning[16] who used beta adrenergic blockade

In accord with the reports by Ebert and co workers[7] and Goodall and Kirshner[13] the myocardial catecholamines were significantly reduced four weeks after BSTG but returned to normal at six months Slightly higher myocardial catecholamines were noted from the non ischemic left ventricle in dogs which died in less than 15 minutes than in those dogs surviving longer than 48 hours These differences might have been present before coronary ligation and so contribute to the protective effect, but were more likely due to some degree of myocardial failure resulting from the extensive myocardial infarction As reported by Russell, Crawford and Harris[24] there was a gradual fall over 48 hours in myocardial norepinephrine in the infarcted ventricle of both BSTG 6 mo and control dogs Myocardial norepinephrine did not correlate with changes in postocclusion heart rate or ventricular arrhythmias Therefore it was not the absolute level of myocardial norepinephrine which produced the protective effect In the BSTG dogs there may have been impaired release of myocardial norepinephrine or lower levels of circulating epinephrine The latter could result from removal of cardiac sympathetic afferent nerves with a decrease in the stimulus to the adrenal medulla following coronary ligation

However, circulating catecholamines were not measured in this study The mechanism by which myocardial norepinephrine levels return to normal after six months in the presence of a functionally adequate sympathectomy is not known It is possible that the sympathetic fibers in the vagosympathetic trunk may anastomose with the denervated sympathetic fibers in the epicardial plexuses and so restore connections with the synaptic vesicles

Assessment of sympathetic regeneration has been neglected in many previous studies Spinal cord stimulation was performed at the level of the second thoracic spinal roots in three BSTG 4 wk , five BSTG 6 mo , and five control dogs The percentage increase in the cardiac rate was an indication of functional sympathetic re innervation The three BSTG 4 wk and five control dogs had a 10 per cent and 78 per cent mean increase in heart rate, respectively With respect to the five BSTG 6 mo animals two dogs had negligible responses (3 3 and 3 8 per cent), two dogs had mild responses (21 9 and 22 5 per cent), and one dog had a near normal response (67 6 per cent) This suggests that only one of the five BSTG 6 mo dogs had functionally significant sympathetic regeneration Since a general anesthetic and major cervical laminectomy were required for spinal cord stimulation, this procedure could only be performed prior to death Also, the five BSTG 6 mo and five control dogs had all survived coronary ligation by longer than 48 hours and were thus a selected sample It was possible that the BSTG 6 mo dogs which developed ventricular fibrillation after coronary ligation might have had functionally more complete sympathetic regeneration and this would account for the higher mortality in our study compared to the results of McEachern, Manning and Hall[2] and Skelton and co workers[1] (Table VIII) Regenerating neural filaments were demonstrated histologically by Bodian's impregnation on the right side in one out of four BSTG 6 mo dogs No regenerating neural tissue was demonstrated in the other seven specimens Thus sympathetic regeneration had occurred at six months after BSTG in an animal which developed ventricular fibrillation This evidence supported the role of the sympathetic nervous system in inducing VF following coronary ligation

Thus a significant protective effect from VF was demonstrated in the early critical period after coronary ligation in dogs which had BSTG performed six months previously The presence of sinus arrhythmia, responses to spinal cord stimulation and histologic evidence of neural regeneration suggested sympathetic re innervation had occurred in 20 to 25 per cent of the dogs

Summary

The effects of left circumflex coronary artery (LCA) occlusion six months after bilateral cardiac sympathectomy on mortality, arrhythmias, and myocardial norepinephrine were studied with functional and histologic assessment of sympathetic regeneration Bilateral stellate ganglionectomy, thoracic sympathectomy, and ansectomy (BSTG) were performed on 23 dogs and denervation was confirmed by electrical stimulation Six months later the LCA was ligated by a two stage technique in these dogs (BSTG 6 mo) and 23 control dogs in the conscious state All dogs were autopsied at death or after 48 hours Mortality at 15 minutes from ventricular fibrillation (VF) was 22 per cent in BSTG 6 mo dogs and 52 per cent in control animals ($p < 0.05$) Mortality in the two groups at 24 hours was 44 per cent and 65 per cent respectively Before LCA occlusion, sinus arrhythmia was present in 23 per cent of the BSTG 6 mo dogs and 82 per cent of the control animals A significantly greater percentage increase in the sinus cardiac rate one minute after LCA occlusion was present in control dogs compared to BSTG 6 mo dogs ($p < 0.005$) There was a later onset of ventricular arrhythmias lesser incidence of ventricular premature beats (VPB) and ventricular tachycardia (VT), and a shorter duration of VT in BSTG 6 mo dogs than in control animals Myocardial norepinephrine levels were similar in BSTG 6 mo and control dogs and fell after coronary occlusion by a comparable degree in the healthy and infarcted ventricles in both groups Upper thoracic spinal cord stimulation (SCS) produced a mean 10 per cent increase in heart rate of three dogs four weeks after BSTG and a 21 per cent increase in five BSTG 6 mo animals in contrast with a 78 per cent increase in five control animals Only one BSTG 6 mo dog showed an almost normal (68 per cent) response to SCS Histologic studies showed neural regeneration on the right side in one out of four BSTG 6 mo dogs Thus after six months BSTG still confered a protective effect from VF following experimental

coronary occlusion in conscious dogs especially in the early most critical period following myocardial infarction Functional and histologic studies demonstrated sympathetic re innervation in 20 to 25 per cent of the BSTG 6 mo dogs

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Electrocardiographic changes in Panamanian *Rattus rattus* naturally infected by *Trypanosoma cruzi*

Roberto Blandon M D
John H Edgcomb M D
J Felix Guevara, M D
Carl M Johnson, M D, Sc D
Panama City Republic of Panama

In parts of central Panama where Chagas' disease is endemic studies of *Rattus rattus* trapped in and near homes have shown that over 50 per cent of those examined were infected by *Trypanosoma cruzi*.[1]

This report describes a method for registering electrocardiograms on rats and presents some electrocardiographic data on *R rattus* including abnormalities attributable to *T cruzi* infection

Methods

Rats trapped alive in areas endemic for Chagas' disease (Santa Rita and Mendoza) and in areas free of Chagas disease (the city of Panama) were brought to the laboratory and kept singly in cages Giemsa stained thick films of tail blood were examined for *T cruzi* About 40 per cent of rats so examined were found to be infected, an additional 15 per cent were shown to be infected by hemoculture or by microscopic examination of the heart postmortem

Electrocardiograms were made on 31 rats with demonstrated *T cruzi* parasitemia and on 11 rats in which *T cruzi* could not be demonstrated The negative rats were from the city of Panama, where Chagas' disease is not endemic To avoid the complication of traumatic cardiac lesions, only those which had not been subjected to cardiac punctures were studied

The animals were lightly anesthetized with ether Electrocardiograms were taken with the rat lying straight on its back with the front legs semi flexed and the hind legs slightly extended The electrodes were No 25 hypodermic needles attached to platinum wire One electrode was placed subcutaneously in each of the paws and the precordial electrode was positioned at three subcutaneous points in the plane bisecting the anteroposterior axis of the thorax (1) at the right margin of the sternum (2) midway between the sternum and the left axillary line and (3) at the left axillary line A team of three people anesthetist electrocardiographer, and a technician to place the electrodes and to position the rat took electrocardiograms at a rate of one every three minutes

The electrocardiograms were registered on a mimeograph model 3 channel machine* at a velocity of 100 mm per second Complete electrocardiograms were registered from five infected and from five noninfected rats Standard leads only were registered from 26 infected and six noninfected rats

Results

An analysis of the electrocardiograms of 31 rats naturally infected with *T cruzi* is presented in Table I and is summarized as follows

Sinus rhythm was present in 27 rats Four rats had abnormal tracings Of these two rats had second degree A V blocks one was 2 1 and intermittent (Fig 1) and the other had a Wenckebach Luciani pattern (Fig 2) A third rat had

From the Department of Clinical Investigation and Pathology Gorgas Memorial Laboratory Panama City Pepublic of Panama

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*Model Cardirex 31 B manufactured by Elema Schonander Co

Table 1 Electrocardiographic analysis of rats with *T cruzi*

Rat No	*Frequency /minute*	*Duration P R (sec)*	*Duration P (sec)*	*Duration QRS (sec.)*	*P-axis*	*QRS-axis (degree)*	*ST/T**
1	400	2 A V	Block	0 020	+30	+30	i
2	5[illegible]0	0 04	0 01	0 015	+60	+30	i
3	448	0 0[illegible]	0 01	0 015	+90	+20	i
4	360	Nodal	Rhythm	0 015	—	+30	i
5	4[illegible]0	0 04	0 01	0 015	+50	+30	i
6	[illegible]0	Aur	Fibr	0 015	—	+60	i
7	340	0 05	0 015	0 02	+30	+30	i
8	472	0 045	0 015	0 015	+30	+60	i
9	500	0 05	0 015	0 015	+60	+90	i
10	344	0 065	0 02	0 02	+90	+75	i
11	440	0 04	0 01	0 015	+60	+10	i
1[illegible]	360	0 045	0 015	0 02	+40	—	i
13	800	0 027	0 01	0 01	+90	+70	d
14	840	0 035	0 01	0 01	+80	+30	d
15	304	0 05	0 015	0 02	+30	+60	i
16	340	0 045	0 02	0 02	+60	+30	i
17	720	0 035	0 01	0 01	+60	+110	i
18	840	0 03	0 01	0 01	+70	+60	d
19	760	0 03	0 01	0 01	—	+30	d
20	840	0 027	0 01	0 01	+60	+60	i
21	460	0 04	0 01	0 0[illegible]	+60	+30	i
[illegible]	[illegible]60	0 04	0 01	0 01	+60	+20	d
23	680/460	2 A V	Block	0 015	—	+60	i
24	480	0 04	0 015	0 015	+90	+90	i
25	620	0 03	0 01	0 01	+[illegible]0	+30	i
26	680	0 03	0 01	0 01	+45	+0	i
27	460	0 05	0 01	0 02	+30	+30	e
28	448	0 05	0 0[illegible]	0 02	+90	+60	e
29	440	0 05	0 015	0 02	+90	+30	i
30	440	0 045	0 015	0 02	+30	+90	i
31	360	0 06	0 015	0 015	+30	+110	e

i, isodiphas c e el ated and d, depressed

nodal rhythm (Fig 3) and a fourth rat had an irregularly irregular rhythm *without recognizable* P waves a pattern of auricular fibrillation (Fig 4)

Cardiac rate The slowest rate observed was 320 beats per minute The fastest was 840 beats per minute

Ventricular rate In most rats the ventricular rate ranged from 400 to 500 beats per minute The one with the slowest ventricular rate was that with auricular fibrillation

Duration of P wave The shortest duration of the P wave was 0 009 second and the longest 0 02 second The duration of the P wave in most rats was 0 015 second.

Duration of P R interval The shortest P R interval was 0 0275 second, and the longest was 0 065 second In most rats the P R intervals varied between 0 03 and 0 04 second.

Duration of QRS complex The least duration was 0 009 second, and the greatest was 0 02 second. The average duration was 0 015 second

P axis In most instances the P axis in the frontal plane was directed to the left and inferiorly between +30 and +60 degrees In six rats it was perpendicular to the horizontal plane (+90 degrees) In the four rats which did not present with sinus rhythm the P axis could not be determined.

QRS axis In most rats the QRS axis like the P axis was directed inferiorly and to the left in the frontal plane In three rats it was perpendicular to the frontal plane (+90 degrees) and in two rats it was directed to the right (+110 de

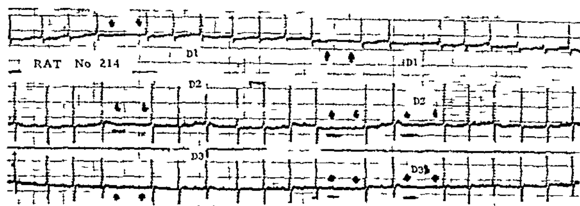


Fig 1 Rat No I 23 Variable rate 460 to 680 beats per minute with and without block Sinus rhythm with intermittent second degree A V block. Note in Lead D_2 that the block is bidirectional in type with P waves negative in the beginning and later positive The P axis cannot be determined. QRS axis +60 degrees Isodiphasic ST segment and T wave The rat had a chronic *T cruzi infection*

Table II Electrocardiographic analysis of 11 rats without demonstrable *T cruzi*

Rat No	*Frequency /minute*	*P R (sec)*	*Duration P (sec)*	*Duration QRS (sec)*	*P-axis*	*QRS axis (degree)*	*ST/T**
1	520	0 040	0 01	0 015	+50	+60	e
2	480	0 050	0 015	0 015	+60	+60	i
3	528	0 040	0 01	0 015	+60	+40	e
4	500	0 045	0 01	0 015	+60	+30	e
5	500	0 072	0 01	0 010	+60	+90	i
6	448	0 070	0 015	0 015	+90	+30	e
7	448	0 045	0 015	0 010	+30	+60	d
8	488	0 045	0 01	0 02	+50	+30	e
9	512	0 040	0 02	0 015	+50	+30	i
10	448	0 040	0 01	0 015	+60	+90	i
11	520	0 050	0 015	0 015	+90	+100	i

i isodiphasic e elevated and d, depressed.

grees) In one rat the axis was parallel to the frontal plane (0 degrees) and in one rat the axis could not be determined

Morphology of the QRS complex Precordial leads were taken in five animals In the right precordial leads patterns rS and QS were present in two rats and a pattern rSr was present in one rat In the left precordial leads the pattern qR was present in two rats and the pattern rS was present in three rats

Size of the cardiac chambers This could be evaluated only in five rats with complete electrocardiograms, i e including precordial leads Two rats had enlargement of the right ventricle (Fig 5) with right axis deviation (+90 and +110 degrees) and rS patterns in the left precordial leads In one rat biventricular enlargement was diagnosed there was right axis deviation a RSR pattern in Lead V_1 and a qR pattern in Lead V_6

For comparison the analysis of the electrocardiographic findings in 11 apparently healthy rats without *T cruzi* infection is presented in Table II and summarized as follows

Rhythm All 11 rats had sinus rhythm

Heart rate The fastest was 528 beats per minute, and the slowest was 448 beats per minute

Duration of P wave The least duration was 0 01 second and the greatest was 0 02 second

Duration of P R interval The least duration was 0 04 second, and the greatest was 0 07 second

Morphology of the QRS complex Of five rats with right precordial leads pattern rSr was present in two rats and patterns Rs rS and RSr were each present in one rat In the left precordial leads of the same five rats pattern qRs was present once Rs twice RS once and qR once

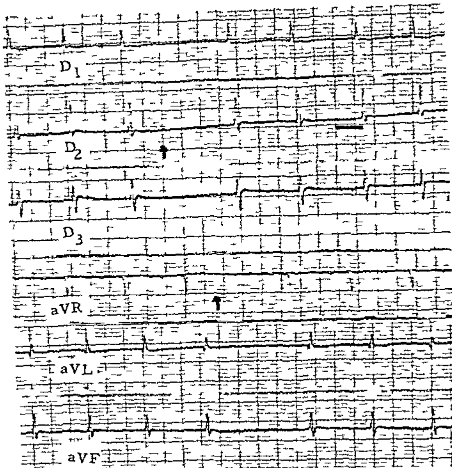


Fig 2 Rat No 11 Second degree A V block Wenckebach Luciani type The arrows mark P waves Rate 400 beats per minute P axis +30 QRS axis +30 Duration of QRS 0 02 second Rat with chronic *T cruzi* infection

P axis In most rats the P axis in the frontal plane was directed to the left and inferiorly In only two rats was it perpendicular to the frontal plane

QRS axis In eight rats the QRS axis in the frontal plane was directed to the left and inferiorly In two rats it was perpendicular (+90 degrees) and in one rat it was directed to the right (+110 degrees)

ST segment and T wave In five rats the ST segment was isoelectric with no apparent T wave In five rats the ST T complex was elevated with upward convexity and in one rat it was depressed.

Discussion

The electrocardiographic methods we used for *R rattus* appear to be satisfactory

Certain differences were found between the electrocardiograms of the group of *R rattus* naturally infected with *T cruzi* and of the group of *R rattus* not infected. These differences are (1) with respect to heart rate in 11 out of 31 infected rats the rate was greater than 520 beats per minute the maximum rate observed in the uninfected rats Moreover seven infected rats had rates less then 400 beats per minute the minimum rate encountered in the uninfected rats (2) Four infected rats had cardiac arrhythmias one auricular fibrillation one nodal rhythm one second degree A V block with intermittent 2 1 pattern and one second degree A V block with Wenckebach Luciani pattern No arrhythmias were encountered in the uninfected rats (3) The duration of the P R interval was much more variable in the group of infected rats than in uninfected rats

No difference between the two groups in the shape or duration of the P wave were noted The orientation of the P and QRS axis to the frontal

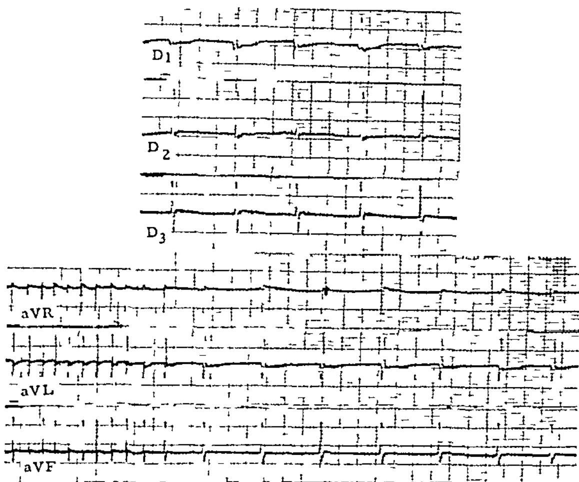


Fig 3 Rat No I 4 Chronic *T cruzi* infection Nodal rhythm (note the absence of P waves) Ventricular rate 360 beats per minute Duration of QRS 0 15 second QRS axis +30 P axis indeterminate ST/T wave isodiphasic

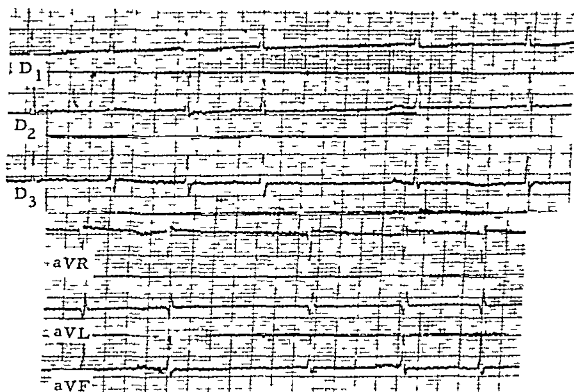


Fig 4 Rat No I 6 Chronic *T cruzi* infection Atrial fibrillation (note P waves of diverse form) Average ventricular rate 320 beats per minute Duration of QRS 0 015 second QRS axis +60 ST/T wave isodiphasic

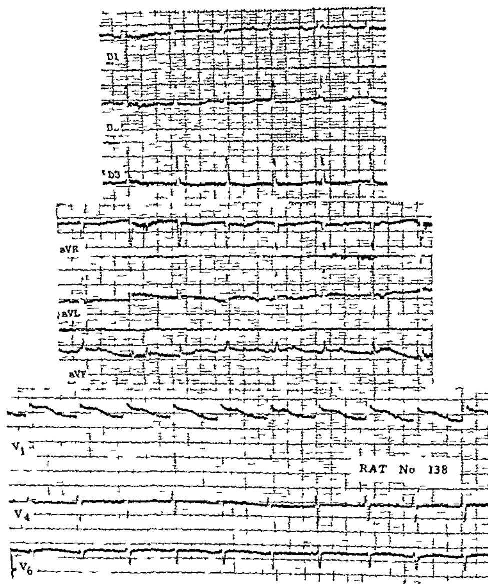


Fig 5 Rat No I 31 Chronic *T cruzi* infection. Sinus rhythm Cardiac rate 360 beats per minute PR, 0 06 second. P wave 0 015 second. P axis +30 QRS axis +110 ST/T wave elevated Lead VI is diagnostic of hypertrophy of the right ventricle (confirmed at necropsy)

plane was the same in the two groups both being most often directed to the left and inferiorly

The criteria of Sambhi and White[2] seem to be of value in the determination of hypertrophy of the cardiac chambers Our limited experience suggests that one cannot detect enlargement of a chamber by examination of only the standard leads, which regularly show the axis oriented to the left and inferiorly with precordial leads one can derive information about the axis in two planes and this information may be useful in detecting enlargement of one or more cardiac chambers

Germiniani and Oliveira e Cruz[3,4] and Sambhi and White[2] agree that the presence in the rat of rSR or rSr patterns which might be considered the patterns of incomplete right bundle branch block do not represent a true block They are instead polyphasic complexes which reflect the effect of the crista supraventricularis on the electrocardiogram The crista supraventricularis seems to be of special importance in the rat for these patterns are not seen in the electrocardiograms of guinea pigs[3]

There are considerable differences between the reported observations of T waves and ST seg

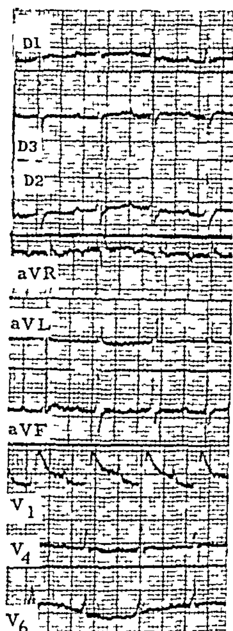


Fig 6 Rat No II 5 Sinus rhythm Frequency 500 beats per minute PR 0 072 second. P wave 0 01 second. QRS 0 01 second P axis +60 QRS axis +90 ST/T complex isodiphasic and elevated. This tracing is considered to be characteristic of a normal adult *R rattus*

ments in rats Germiniani and Oliveira e Cruz[3] found elevation of the ST segment to be present in all normal electrocardiograms of laboratory rats (*R norvegicus*) They considered the constancy of this finding to be of use in distinguishing the electrocardiograms of rats from those of guinea pigs But Sambhi and White [2] working with Long Evans rats reported that the normal electrocardiogram was characterized by an absence of an ST segment They considered that this absence might be misinterpreted to represent displacement of the ST segment and broadening of the S wave consistent with complete right bundle branch block

Germiniani and Oliveira e Cruz[3,4] studied *R norvegicus* of the Wistar laboratory strain, and Sambhi and White[2] studied *R norvegicus* of the Long Evans strain We have studied *R rattus* because this species is naturally infected with *T cruzi*. In our study of uninfected rats we found elevated ST segments in five out of 11 rats and a depressed ST segment in one rat and in five rats the ST segment was isoelectric with no apparent T wave This latter pattern predominated in infected rats (Table I) In three infected rats, the ST segment was elevated with superior convexity and fused with the T wave (resembling hypopotassemia), and in five rats the ST segment and T wave were depressed (somewhat similar to digitalis effect)

The four types of arrhythmia found in infected animals were supraventricular in origin Neither ectopic beats nor bundle branch blocks were encountered although both of these abnormalities are often present in human patients with chronic Chagas disease

Summary

A simple, rapid method of performing electrocardiography on anesthetized rats is described The electrocardiograms of 31 *R rattus* naturally infected with *T cruzi* and of 11 uninfected *R rattus* are described The most common abnormalities of infected rats were tachycardia, bradycardia, and supraventricular arrhythmias

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Anti arrhythmic effects of lidocaine metabolites

Robert G Burney M D
Cosmo A DiFazio M D Ph D
Michael J Peach Ph D
Kent A Petrie
Michael J Silvester
Charlottesville Va

Lidocaine has been used extensively as an anti arrhythmic agent particularly in the treatment of postmyocardial infarction patients In these patients plasma concentrations of 1 to 5 μg per *milliliter are sought as* therapeutic anti arrhythmic levels [1] In a series of postmyocardial infarction patients receiving intravenous lidocaine infusions two de ethylation products of lidocaine (Fig 1), monoethylglycine xylidide (MEGX) and glycinexylidide (GX) have also been observed in plasma [2,3] Significant anti arrhythmic activity of either of these metabolites would contribute to the therapeutic effects attributed to intravenous lidocaine Smith Duce and Boyes[4] reported that the peak anti arrhythmic effect *of orally* administered lidocaine occurs *after* the peak plasma levels of lidocaine supporting the hypothesis that some metabolite seems to be exerting an anti arrhythmic effect Cardiac effects of MEGX have been demonstrated [5,6]

The purpose of the present study was to compare the antiarrhythmic effects of lidocaine MEGX and GX in clinically appropriate concentrations and to determine *their* dose response relationships

Methods

A guinea pig atrium model was chosen as designed by Peach and Chiu [7] The protective effects of lidocaine and MEGX on ouabain induced arrhythmias were studied in the range of clinical therapeutic *concentrations* 1 to 3 μg per milliliter GX was studied over a larger range 1 to 9 65 μg per milliliter in order to establish its effect

All experiments were done using male *albino* guinea pigs 400 to 600 grams in weight Each animal was anesthetized with either sodium pentobarbital (30 mg per kilogram, intraperito*neally) or sodium* thiopental (50 mg per kilo

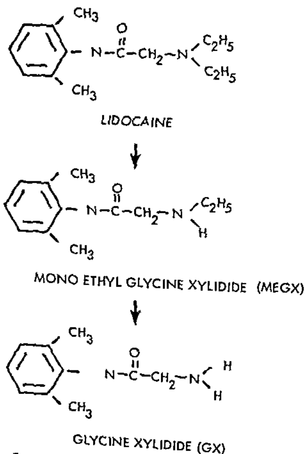


Fig 1 Partial metabolic pathway for lidocaine

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R print reque ts Dr Robert G Burney University f Virgin a M di l Cente Cha lotte ville Va 2?903

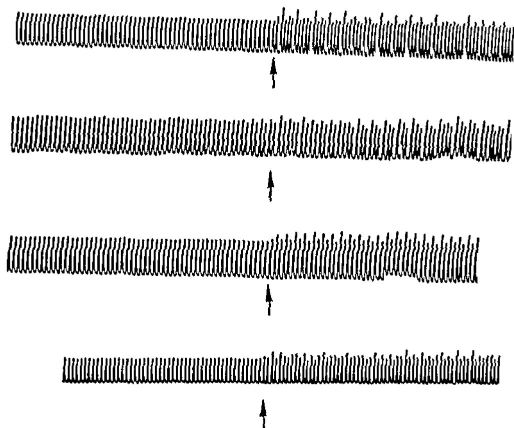


Fig 2 Sample records Onset of the arrhythmia is indicated by the arrow under each record

gram intraperitoneally) The thoracic cage was opened and the right atrium was extracted with the *sino artial node and appendage intact* The atrial strips were hung in an 8 ml glass chamber filled with Krebs Henseleit solution maintained at 37° C and bubbled with a 95 per cent O_2 5 per cent CO_2 gas mixture The resulting pH was 7 4 Spontaneous atrial contractions were recorded on a Grass Model 5 Polygraph via Statham force transducer One gram resting tension was maintained on the strips During an equilibration period of at least 40 minutes the preparations were washed every five minutes until stable resting heart rates were attained Stable conditions were defined as a constant force of contraction with a rate between 180 and 220 beats per minute with a variation of less than 6 beats per minute

After equilibration concentrated solutions of lidocaine HCl (epinephrine free), MEGX or GX in Krebs Henseleit solution were added to the bath to produce final bath concentrations of 1 to 3 1 μg per milliliter (lidocaine and MEGX) and 1 to 9 6 μg per milliliter (GX) Lidocaine, MEGX, and GX bath concentrations were assayed by gas chromatography [8] The preparations were allowed to stand three minutes Then a 15 μl bolus of ouabain (0 25 mg per milliliter) was added to the bath and allowed to equilibrate for ten minutes. After this period, 10 μl of dilute ouabain (0 025 mg per milliliter) were added at three minute intervals until an arrhythmia was produced An arrhythmia (Fig 2) in this experimental model was defined as an irregularity in heart rate seen for a period of not less than five minutes A control point for the production of arrhythmias without protective drugs was established by using the above procedure with each group of animals Each preparation was used only once to prevent possible cumulative drug effects

Results

Arrhythmias were consistently produced with ouabain alone before introducing any protective drugs The concentration of ouabain necessary to produce an arrhythmia without other drugs (control) and with various concentrations of lidocaine MEGX, and GX are listed in Table I An arrhythmia was consistently produced in the absence of protective drugs with ouabain (0 486 ± 0 014 μg per milliliter) Increasing concentrations of protective drugs resulted in a linear in

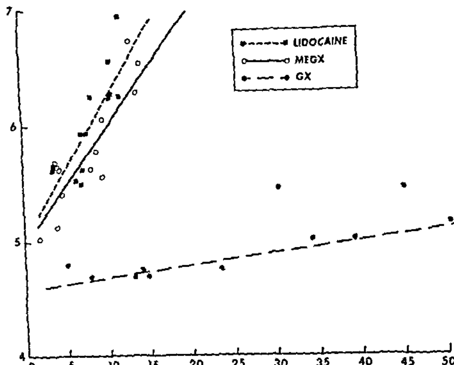


Fig 3 Graph of data in Table I showing essentially identical protective effects of lidocaine and MEGX and much lower potency of GX. Ouabain concentration in μg per milliliter is shown on the ordinate Protective drug concentration (μmolar) is shown on the abscissa

crease in the concentration of ouabain required to produce an arrhythmia (Fig 3) The slopes of the regression lines for the protective effect for lidocaine and MEGX were essentially the same 0 012 vs 0 010 The potency of MEGX in comparison to lidocaine was calculated to be 0 833 1 In contrast the slope of the GX curve (0 001) was much lower indicating that the second de ethylation resulted in a much less potent anti arrhythmic agent The calculated potency of GX was about 1/10 that of lidocaine

Discussion

The purpose of this study was to determine if the two de ethylation metabolites of lidocaine (MEGX and GX) could significantly contribute to the anti arrhythmic effect seen during lidocaine infusion Smith Duce and Boyes[4] reported that the peak anti arrhythmic effect was seen later than the peak lidocaine blood level after oral administration of lidocaine This would suggest that a metabolite is contributing to the anti arrhythmic effect. When MEGX was measured in seven patients receiving intravenous lidocaine blood levels of 0 83 ± 0 80 μg per milliliter were found with a range of 0 31 to 2 60[2] It is not clear whether the wide range of these values is due to variations in time of sampling liver function cardiac output or other factors Significant concentrations of MEGX are to be expected when a lidocaine infusion is given. Beckett, Boyes and Appleton[10] estimated from a computer model that after two hours 12 per cent of the injected dose is present as MEGX, whereas 45 per cent remains as lidocaine In an unpublished study by the authors (RGB and CDF) of a patient on prolonged epidural block MEGX blood levels were 24 to 41 per cent of the corresponding lidocaine level In dogs observed for two hours after a bolus lidocaine infusion lidocaine levels were found to consistently decrease while MEGX which is formed from the metabolism of lidocaine peaked and remained relatively constant in the period from 30 minutes to the two hours of observation after the lidocaine administration[9] At two hours the lidocaine and MEGX levels were essentially equal

MEGX in this study was found to be approxi

Table I Ouabain concentrations needed to produce arrhythmias with and without protective drugs

Control		*Lidocaine*			*MEGX*			*GX*		
Drug Conc	Ouabain to in duce arrhyth *μg/ml*	Drug Conc *μg/ml*	Drug Conc *μmolar*	Ouabain to in duce arrhyth *μg/ml*	Drug Conc *μg/ml*	Drug Conc *μmolar*	Ouabain to in duce arrhyth *μg/ml*	Drug Conc *μg/ml*	Drug Conc *μmolar*	Ouabain to in duce arrhyth. *μg/ml*
0 00	0 469	0 94	3 55	0 563	0 39	1 77	0 503	0 96	5 00	0 481
0 00	0 469	0 94	3 55	0 563	0 86	3 91	0 569	1 88	7 79	0 469
0 00	0 481	1 00	3 78	0 566	0 88	4 00	0 513	2 50	13 01	0 469
0 00	0 494	1 66	6 27	0 553	0 90	4 09	0 566	2 68	13 95	0 475
0 00	0 500	1 83	6 92	0 550	0 95	4 32	0 563	2 81	14 63	0 469
0 00	0 500	1 88	7 11	0 594	1 02	4 63	0 541	4 48	23.32	0 475
Mean	0 486	1 88	7 11	0 563	1 78	8 08	0 563	5 80	30 20	0 544
± S D	0 014	1 98	7 48	0 594	1 94	8 81	0 578	6 56	34 15	0 500
		2 22	8 39	0 625	2 09	9 49	0 556	7 52	39 15	0 500
		2 81	10 62	0 656	2 14	9 72	0 606	8 64	44 98	0 544
		2 81	10 62	0 625	2 89	13 13	0 672	9 65	50 23	0 513
		2 88	10 88	0 628	3 04	13 81	0 626			
		3 12	11 79	0 625	3 14	14 26	0 653			
		3 12	11 79	0 694						

mately 80 per cent as potent an anti arrhythmic agent as lidocaine and in other studies MEGX has been reported to have 30 and 60 per cent of the potency of lidocaine on the heart[5,6] It would appear the MEGX which is formed from lido caine and appears in significant concentrations does contribute to the total anti arrhythmic effect In contrast, GX was observed to have ap proximately 1/10 the anti arrhythmic potency of lidocaine and even when it is present in equal blood concentrations, would have only a minimal contribution on the total anti arrhythmic effect seen with lidocaine administration

Drugs with local anesthetic properties usually have anti arrhythmic effects Since GX is a pri mary amine and primary amines are poor local anesthetics it is not surprising that this agent is also a weak anti arrhythmic drug In contrast the first de ethylation product of lidocaine (MEGX) maintains local anesthetic activity and has anti arrhythmic properties It would appear from this study that the MEGX formed in the metabolism of lidocaine may explain the discre pancy between the peak anti arrhythmic effects and the peak lidocaine blood levels reported by Smith Duce and Boyes[4] Since the relative tox icity of MEGX is approximately that of lido caine[11] MEGX does not offer any advantages as an anti arrhythmic agent however its presence should be considered in the clinical evaluation of lidocaine therapy for arrhythmias

Summary

Patients on lidocaine infusions for the control of arrhythmias accumulate significant concen trations of lidocaine metabolites The potency of lidocaine in suppressing digitalis induced ar rhythmias in guinea pig atria was compared to that of two of the metabolites of lidocaine mono ethylglycinexylidide (MEGX), and glycinexylidide (GX) The potency of MEGX relative to lidocaine was 0 833 GX was only 1/10 as potent Thus it would seem that MEGX may contribute to the total anti arrhythmic effect of a lidocaine infu sion

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Myocardial alterations following hypothalamic stimulation in the intact conscious dog

Richard E Hall, Ph D
Harley D Sybers M D , Ph D
Jerry H Greenhoot, M D
Colin M Bloor, M D
La Jolla, Calif

Certain electrocardiographic abnormalities, e g , S T segment changes, T wave alterations and prolonged Q T intervals, suggesting recent myocardial infarction have been reported in patients with subarachnoid hemorrhage [1 3] In addition patients who died with subarachnoid hemorrhage in the region of the hypothalamus have had multifocal regions of myocardial necrosis at autopsy [3] These investigators postulated that these electrocardiographic (ECG) abnormalities and myocardial lesions were due to a relative myocardial hypoxia, caused by disproportionate changes in coronary blood flow and cardiac work and by the local release of catecholamines after hypothalamic stimulation However, Rushmer[4] asserted that stimulation of particular sites in the central nervous system can elicit changes almost completely restricted to a single feature of cardiac function If an appropriate site were present in the hypothalamus an alternative explanation of the ECG and myocardial changes would be a selective reduction of coronary blood flow leading to myocardial hypoxia

The pathogenesis of these changes has been explored in the experimental animal These studies included (1) administering large doses of catecholamines [5 7] (2) increasing intracranial pressure,[1 8 9] and (3) electrically stimulating central nervous system structures [3 10 11] Although these experimental studies produced similar ECG abnormalities and myocardial lesions, the levels of electrical stimulation and catecholamine doses needed to induce these changes exceeded physiologic levels The use of anesthesia and neuromuscular blocking agents in these studies obscured the possible role of central nervous system stimulation in inducing these changes in the conscious animal and the clinical setting The purpose of our study was to electrically stimulate the posterior hypothalamus at physiologic levels in the conscious dog and to monitor the changes induced in the ECG and systemic and coronary hemodynamics Postmortem studies were conducted to correlate morphologic changes in the myocardium with the hemodynamic changes

Materials and methods

Animal preparation Physiologic studies were conducted using an unanesthetized animal preparation in which cerebral stimulating electrodes were chronically implanted The general surgical procedures were similar for the six dogs studied. Mongrel dogs (20 to 30 kilograms) were anesthetized with halothane supported on a Harvard respirator and placed in a stereotaxic apparatus Bipolar stainless steel electrodes (O D 0 008 inch, Teflon coated) were implanted bilaterally into the posterior hypothalamic area according to the stereotaxic atlas of Lim, Liu and Moffitt [12] The co ordinates were rostral, 18 mm , lateral 1 5 mm , and 10 5 mm above the Horelay Frankfort plane After a one week recovery period, the dogs were again anesthetized subjected to a left thoracotomy, and had a polyvinyl

From the Departments of Neurosciences Pathology and Neurosurgery University of California—San Diego School of Medicine La Jolla

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Reprint requests to Dr Colin M Bloor Department of Pathology UCSD School of Medicine La Jolla Calif 92037

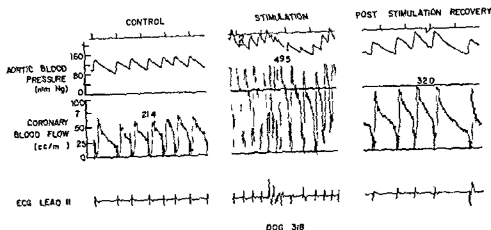


Fig 1 Phasic hemodynamics and ECG Lead II Record from a dog with stimulating electrodes implanted in the hypothalamus. Left to right panels are control stimulation and poststimulation recovery Stimulus was 100 Hz. for 1 0 msec at 0 6 ma Notice the premature ventricular contractions elicited during stimulation and their persistence during the poststimulation recovery Time marks (top tracing) 1 sec Recording speed, 50 mm. per second

catheter implanted in the aorta to measure blood pressure and heart rate Aortic pressure was determined with an Elema Schönander transducer and the heart rate was determined via a Lead II ECG Data were recorded continuously with a 12 channel high frequency response Elema Schönander Mingograf ink jet recorder After a four day recovery period, the animals were monitored for a period of two weeks to obtain control data

Experimental design A Grass S 88 stimulator was used to deliver biphasic rectangular pulses of 1 0 msec duration at intensities of 0 2 to 1 5 ma and a frequency of 100 Hz. Occasionally other frequencies were used (10 to 100 Hz) to check for variations due to frequency Current was monitored on a Tektronix R564B oscilloscope

The dogs were separated into three groups of two dogs each based upon the time lapse between the initial period of hypothalamic stimulation and the time at which the animals were killed. The animals had one period of hypothalamic stimulation and were killed at 4 72 and 168 hours after this stimulation with an overdose of sodium pentobarbital Each period of stimulation comprised twenty episodes each lasting 10 to 20 seconds with five to ten minute intervals between each episode

The two dogs killed at 168 hours were also instrumented with Biotronex electromagnetic flow probes on the aortic root and left circumflex coronary artery at the second operation Coronary artery and aortic blood flows were measured

Table 1 Hemodynamic effects of hypothalamic stimulation

	Heart rate (beats/min.)	Aortic blood pressure (mm. Hg)
Control	103	124
Stimulation	186	209
	83 ± 31†	85 ± 17
P <	0 025‡	0 001

Values are means (N = 6) and represent controls and maximum heart rate responses observed after hypothalamic stimulation
†Mean difference ± standard error of mean difference between mean values of the experimental and control groups
‡Significance of the differences between mean values of the experimental and control groups were tested using a two-tailed Student's t test for paired observations.

using Biotronex BL 310 electromagnetic flowmeter amplifiers The flow probes were calibrated by passing measured flows of whole blood through the flowmeter probes before implantation and the procedure was repeated after removing the probes from the animals at the termination of the experiment Calibration factors for all animals remained constant plus or minus 5 per cent during the study Aortic and coronary blood flows and mean aortic pressure were obtained by integrating the phasic flow and pressure recordings Coronary and systemic hemodynamics were calculated as described before [13,14] Some data was analyzed using a hybrid computing system [15] Systemic and coronary hemodynamics were monitored before, during and up to

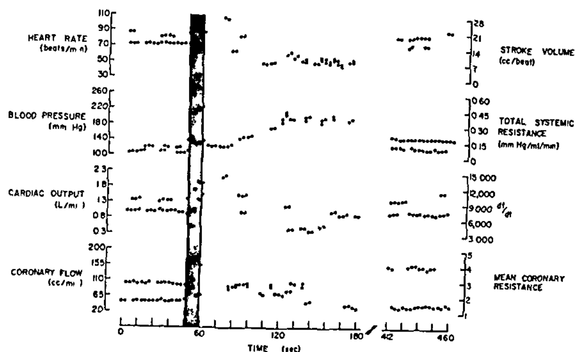


Fig 2 Graph of representative hemodynamics Each point represents the mean value for 3 seconds calculated by hybrid computer Open circles (O) represent left hand ordinate and closed circles (●) represent right hand ordinate Stippled area indicates hypothalamic stimulation period df/dt = acceleration of aortic blood flow

eight minutes after each hypothalamic stimulation episode and thereafter at daily intervals during the experiment

Postmortem studies After the animals were killed, the hearts and brains were fixed The hearts of those animals killed at four hours were fixed for electron microscopy The dogs were anesthetized with sodium pentobarbital and maintained on a Harvard respirator We opened the thorax at the left fifth intercostal space and isolated the aorta, post cava, and right atrium After transecting the post cava and right atrium, we inserted a large bore cannula into the aorta and perfused it with phosphate buffered saline at a pressure of 130 mm Hg After the venous effluent cleared we changed the perfusate to freshly prepared 4 per cent buffered glutaraldehyde After several minutes of perfusion we removed the hearts from the animals and cut small samples from the apex, interventricular septum, and posterior papillary muscle of the left ventricle Only specimens from the 4 hour group were studied by electron microscopy The hearts from animals killed at 72 and 168 hours were fixed in a similar manner except 10 per cent formalin was used as the perfusate Two dogs, similarly instrumented but not subjected to hypothalamic stimulation had their hearts fixed for electron microscopy to serve as control animals

Myocardial tissue samples from all animals were studied by light microscopy using hematoxylin and eosin and Masson trichrome stains All dog brains were fixed in 10 per cent formalin and the electrode sites were verified using Nissl stained whole brain coronal sections.

Results

During the control period, heart rate and aortic blood pressure averaged 93 ± 6 (S E M) beats per minute and 120 ± 7 mm Hg, respectively In the two dogs instrumented with flow probes, cardiac output and resting coronary blood flow were 1 42 ± 0 4 L per minute and 31 ± 6 ml per minute These controls values were similar to those previously described in the conscious dog [13,14]

Physiologic changes during and after hypothalamic stimulation Immediately upon hypothalamic stimulation there was a sinus tachycardia in all dogs that persisted during stimulation During and immediately after stimulation other ECG changes occurred in three dogs These included T wave inversions subsequent increases in T wave amplitude, and multi focal premature ventricular contractions (Fig 1) The ECG's of all dogs had returned to normal sinus rhythm within 15 minutes of completion of the stimulation During stimulation of the posterior hypothalamus heart rate and aortic blood pressure in



Fig 3 Electron micrograph of myocardial tissue These are typical single cell lesions found four hours after hypothalamic stimulation The myofilaments have condensed to form contraction bands (×4 800)

creases significantly above control values in all dogs (Table I) The magnitude of heart rate changes during stimulation varied between animals

In the two dogs instrumented for cardiac output and coronary blood flow measurement hemodynamic changes were monitored during twenty stimulation episodes each Fig 2 shows a representative continuous recording of hemodynamic parameters before during and after posterior hypothalamic stimulation in one experiment The narrow range of values before and seven to eight minutes after stimulation shows the stability of the conscious animal model and the marked changes that occurred during and immediately after stimulation With the onset of stimulation heart rate aortic blood pressure cardiac output and coronary blood flow increased Initially stroke volume and acceleration of aortic flow (df/dt) dropped, but then rose above control levels The increased coronary flow was associated with increases in both systolic and diastolic coronary flow When stimulation ceased, these parameters gradually returned to control levels except aortic blood pressure which remained elevated for several minutes. This resulted in a delayed rise in calculated systemic and coronary resistances suggesting that there had been a delayed reflex vasoconstriction By seven to eight minutes after stimulation these cardiovascular parameters were at control levels and remained there for the duration of the study

Pathologic changes after hypothalamic stimulation Locations of the stimulating electrodes were verified in each animal using Nissl stained whole brain coronal sections All were located in the posterior hypothalamic region On microscopic examination there was mild gliosis and edema in the immediate vicinity of the electrode capsule but there was no evidence of extensive necrosis or invasion of microglia which would have suggested traumatic injury caused by the stimulation

In the two animals killed four hours after posterior hypothalamic stimulation light microscopic examination showed no lesions in the myocardial samples which were obtained from the apex interventricular septum and posterior papillary muscle of the left ventricle But on electron microscopy focal lesions were



Fig 4 Electron micrograph of myocardial tissue This slightly tangential cut reveals slightly dilated tubules of the sarcoplasmic reticulum (×21 000)

present subendocardially in all samples from these sites (Figs 3 and 4) These lesions comprised discrete foci of necrosis involving one or two cells while immediately adjacent cells were normal The necrotic cells showed myofibrillar degeneration and contraction band formation Their mitochondria were swollen and contained flocculant precipitates In addition tubules of the endoplasmic reticulum were slightly dilated

In those animals killed 72 and 168 hours after stimulation, light microscopic examination showed focal lesions in perivascular and subendocardial regions of the myocardial samples (Figs 5 and 6) These lesions comprised foci of granulation tissue composed of loosely packed, elongated nuclei of fibroblasts and endothelial cells interspersed between groups of normal myocardial cells A cellular infiltrate accompanied the zones of granulation tissue In those animals killed 72 hours after stimulation the cellular infiltrate was dense and contained many polymorphonuclear leukocytes as well as some lymphocytes and plasma cells In those animals killed 168 hours after stimulation the cellular infiltrate was predominantly mononuclear In myocardial samples obtained from the interventricular septum the granulation tissue foci were located perivascularly (Fig 5) while in the other samples the lesions were located subendocardially (Fig 6) All myocardial samples obtained from similar sites in the hearts of the two control dogs were normal on electron and light microscopic examination

Discussion

Previous studies using electrical stimulation of central nervous system structures were done in anesthetized animals[3,10,11,16] required stimulation levels in excess of physiologic levels to produce myocardial injury,[3,10,11,16] or did not conduct morphologic examination of the myocardium[16] Thus extrapolation of the significance of these results to the clinical setting has been difficult. Our study was undertaken to see if physiologic stimulation of the posterior hypothalamus could induce myocardial injury and, if so to define the pathogenic mechanisms involved

Several mechanisms have been proposed for the pathogenesis of myocardial injury after posterior hypothalamic stimulation These in

clude (1) induced parasympathetic overactivity[17] (2) induced sympathetic overactivity with local catecholamine release[3,10] (3) reflex induced coronary vasoconstriction[4] and (4) a disproportionate ratio of oxygen supply and demand in the myocardium[18] Groover and Stout[17] showed that myocardial lesions induced by direct vagal stimulation can be prevented by pretreatment with atropine This supports the view of Cropp and Manning[2] that parasympathetic overactivity results in vagal mediated electrocardiographic changes that are suggestive of myocardial ischemia The findings of other observers support the view that sympathetic activity with local catecholamine release is responsible for the induced injury For example Greenhoot and Reichenbach[3] demonstrated myocardial lesions in cats after stimulating the midbrain reticular formation These lesions comprised acute myofibrillar degeneration and granular banding of the cytoplasm progressing into large zones of myocardial cell loss. The fibrosis and mononuclear cellular infiltrates resembled the lesions seen after catecholamine induced myocardial injury[5,19] Other supportive evidence for this view is the finding by Outschoorn and Vogt[0] of increased norepinephrine content in coronary sinus blood during stimulation of the nerve accelerantes Such myocardial injury could result from myocardial ischemia secondary to reduced coronary blood flow caused by reflex induced coronary vasoconstriction[4] The fourth proposed mechanism is that of an imbalance between oxygen supply and demand. Although catecholamine release increases coronary blood flow it also increases the oxygen requirements of the myocardial tissue[21] This could cause an imbalance between oxygen demand and oxygen availability in the myocardium, leading to relative hypoxia and subsequent injury[18]

Our findings shed light on the pathogenesis of these lesions Since an increase in coronary blood flow including both systolic and diastolic portions occurs immediately upon stimulation reflex induced coronary vasoconstriction is *not* a possible mechanism The changes seen in the hemodynamic parameters i e the increases in heart rate mean aortic pressure cardiac output, stroke volume and coronary blood flow with stimulation resemble those induced by catecholamine release or stimulation[21] Since the myocardial lesions we observed by electron and light

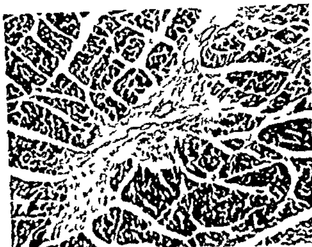


Fig 5 Photomicrograph of myocardial interventricular septal tissue stained with Masson trichrome This is a typical perivascular myocardial lesion present in the interventricular septum of a dog killed 168 hours after hypothalamic stimulation It comprises loss of myocardial fibers interstitial edema capillary dilation vacuolization and cellular infiltrate that is predominantly mononuclear and interspersed fibroblasts (×320)



Fig 6 Photomicrograph of subendocardial tissue stained with Masson trichrome This is a typical subendocardial lesion present in a dog killed 168 hours after hypothalamic stimulation It consists of focal loss of myocardial fibers with replacement by granulation tissue and fibroblasts A scattered cellular infiltrate of lymphocytes and plasma cells is present (×160)

microscopy are similar to those described after catecholamine induced injury[5,19] this mechanism is very likely responsible

Our finding that physiologic levels of stimulation of the posterior hypothalamus in the unanesthetized dog can induce myocardial injury is of particular interest, since similar stimulations of unanesthetized cats conducted daily for periods ranging up to two months have induced even more extensive myocardial injury[22] The in

teresting possibility is raised that chronic central nervous system stimulation may play a role in the pathogenesis of the patchy, interstitial myocardial fibrosis that is occasionally seen at autopsy in patients with minimal coronary artery disease Consideration of these possibilities in future clinical investigations seems desirable

Summary

We sought to determine if electrical stimulation of the posterior hypothalamus at physiologic levels could induce myocardial injury in the unanesthetized dog Biphasic pulses of 1 0 msec. duration, 100 Hz, and 0 2 to 0 8 ma intensity for 15 sec via stereotaxically implanted electrodes in six unanesthetized dogs immediately increased heart rate (95 per cent) and mean aortic blood pressure (73 per cent) In two dogs instrumented for aortic and coronary blood flow measurements, stimulation immediately raised cardiac output (21 per cent) and coronary blood flow (185 per cent) All parameters returned to control within 8 to 10 minutes after stimulation In two dogs killed four hours after stimulation electron microscopy revealed foci of discrete single cell degeneration In two dogs killed 72 and 168 hours after stimulation light microscopy showed multiple foci of myocytolysis and fibrosis located perivascularly and subendocardially These lesions resembled catecholamine induced injury or myocardial lesions secondary to hypoxia The electron microscopy findings suggest that the lesions are catecholamine induced These results suggest that physiologic stimulation of the hypothalamus plays a role in some types of myocardial injury

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Case reports

Ventricular tachycardia in a child An indication for angiocardiography?

Peter D Caldwell M D
Howard J Ricketts M D
David H Dillard, M D
Warren G Guntheroth M D
Seattle Wash.

Primary cardiac tumors have been reported as a cause of ventricular tachycardia in the pediatric age group but clinical data is scarce in the literature To date only eight cases have been reported, and in more than half of these the correct etiologic diagnosis was not made prior to postmortem examination Survival following removal of an intramural ventricular tumor presenting with tachycardia has been described only once [1] The purpose of this report is to present an additional case in which clinical suspicion on these grounds followed by angiographic confirmation led to surgical intervention with a successful outcome

Case report

A four year-old boy with a history of brief bouts of ventricular tachycardia for six months was admitted for evaluation He had been placed on quinidine 150 mg three times a day initially with satisfactory control The child had been so asymptomatic that recommended cardiac evaluation had been deferred by the parents in order to allow for a prolonged summer vacation trip On the morning of admission the patient was found to be pale weak and dyspneic He improved on the way to the family physician s office where an ECG revealed intermittent ventricular tachycardia

On admission to the hospital he was a healthy appearing boy whose heart rate was 110 and irregular The blood pressure was 100/70 and the lungs were clear Cardiac findings were unremarkable with the exception of a Grade 2/6 systolic ejection murmur at the upper left sternal border The remainder of the physical examination was within normal limits Laboratory studies including an erythrocyte sedimentation rate were normal A chest film (Fig 1) revealed an abnormal bulge in the left heart border just above the cardiac apex This region did not pulsate paradoxically by fluoroscopic examination The ECG (Fig 2) showed runs of ventricular tachycardia with interspersed sinus beats Q waves were prominent in V_5 and V_6 suggesting the possibility of an apical infarct.

Right heart catheterization was within normal limits Biplane cineangiocardiography with injection in the main pulmonary artery revealed a normal sized left ventricle with a filling defect near the apex which corresponded with the posterolateral bulge of the left heart border (Fig 3) The left anterior descending coronary artery passed external to the lesion thus establishing the mass as intramural and not pericardial There was minimal encroachment into the apical ventricular cavity and no evidence of tumor mobility or calcification.

Two weeks later the patient was taken to surgery and

From the Departments of Pediatrics Radiology and Surgery University of Washington School of Medicine Seattle Wash.

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Reprint requests to W G Guntheroth M D Department of Pediatrics University of Washington School of Medicine Seattle Wash. 98195

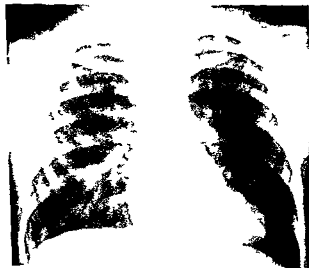


Fig 1 Preoperative thoracic roentgenogram showing abnormal left heart contour with bulge in apical region

I II III aVR aVL aVF

V1 V2 V3 V4 V5 V6

Fig 2 Top and bottom Electrocardiograms Top Preoperative Lead II showing multiple ventricular ex trasystoles and brief runs of ventricular tachycardia Bottom Postoperatively demonstrating normal sinus rhythm with persistent Q waves in V_5 and V_6 with T wave inversion



Fig 3 Cineangiocardiogram showing filling defect (*arrow*) which corresponds to bulge of left heart border

utilizing cardiopulmonary bypass open heart excision of a left ventricular tumor was performed A firm slightly irregu lar 2 ½ by 4 cm mass was present in the free wall of the left ventricle near the apex (Fig 4) There was no approximation to any major coronary artery The lesion did not appear to invade the surrounding myocardium and had a pseudocap sule An incision was made overlying the mass and following mobilization with blunt and sharp dissection excision was accomplished with only minimal entrance into the left ven tricular cavity (Fig 4) There was no evidence of any other lesion and the defect was closed primarily There were no significant postoperative complications and the boy was dis charged in normal sinus rhythm

The final pathological diagnosis was a fibrous hamartoma On cut section the tumor was firm lobular and white (Fig 5) Hi tologically it was composed primarily of fibrous tissue with incorporated bundles and fibers of myocardium as well as elastic tissue (Fig 6)

In the four months since surgery the patient has been asymptomatic and active with no recurrent arrhythmias An ECG obtained two weeks postoperatively (Fig 2) showed sinus rhythm with Q waves and T wave inversion in V_5 and



Fig 4 Left and Right Operative findings Left apex of the heart elevated showing mass in free wall of left ventricle Right Tumor following mobilization showing size of the lesion and extent of left ventricular defect

V_6 compatible with an apical myocardial injury T wave abnormalities were less pronounced in a more recent tracing

Discussion

At the present time there are approximately sixty six reported cases of ventricular fibroma and of these eighty nine per cent occurred in children Successful removal has been accomplished in fourteen cases since the first case with survival was described by Parks and associates[2] in 1962

There has been some degree of confusion in pathological terminology relative to these tumors but in general the case reported here would seem to fit best in the group of lesions classified as fibromas Grossly it resembled a uterine fibroid, an observation which has been made quite frequently in the past in these cases Bigelow and co workers[3] concluded that this tumor arises from primitive cardiac mesenchyme which further differentiates into various connective tissue components This observation could explain the presence of cardiac muscle elements as well as elastic tissue found in this neoplasm

Cardiovascular signs and symptoms were present in 50 per cent of 36 cases of intramural ventricular fibroma reviewed by Geha and associates[4] in 1967 In 30 per cent of these patients the presence of the fibroma was associated with sudden death presumably due to tumor encroachment on the conducting system More recently with increased clinical awareness and improved methods of diagnosis the detection of these tumors has been accomplished more frequently In six of the last eleven cases of ventricular fibroma with successful operative removal ascertainment was primarily through evaluation of murmurs in asymptomatic children who proved to have suggestive roentgenological and ECG abnormalities

Arrhythmias associated with ventricular tumors in children have been primarily ventricular in origin although there are reports of paroxysmal and supraventricular tachycardia in several cases [4,7] In the majority of patients with ventricular tachycardia the correct diagnosis was not suspected prior to death Early demise following onset of tachycardia was the result in several cases [8,9] James and Stanfield[10] described a four year old child with paroxysmal tachycardia in whom the premortem diagnosis was probably endocardial fibroelastosis A previously asymptomatic one and a half year old boy presented with ventricular tachycardia in the case reported by Knieriem and Nessler [11] but the presence of a left ventricular fibroma was not detected until after the patient s death at the age of six years In the series of tumors reported by Simcha and co workers [12] a two and a half year old boy was found to have a right ventricular tumor at the time of internal cardiac massage following cardiac arrest after a prolonged episode of ventricular tachycardia Two cases[13,14] were diagnosed preoperatively but were found to be unresectable at surgery Van der Hauwaert[1] described the only other case in which bouts of tachycardia led to detection by angiography and subsequent successful removal

In some cases another clue for diagnosis can be found on the chest roentgenogram In

I II III aVR aVL aVF

V1 V2 V3 V4 V5 V6

Fig 2 Top and bottom Electrocardiograms Top Preoperative Lead II showing multiple ventricular extrasystoles and brief runs of ventricular tachycardia Bottom Postoperatively demonstrating normal sinus rhythm with persistent Q waves in V_5 and V_6 with T wave inversion



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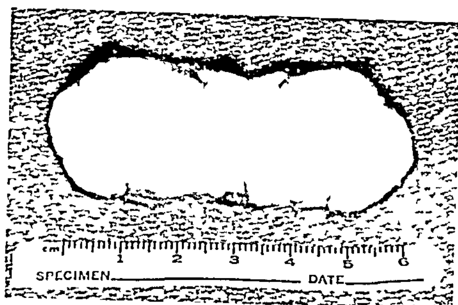


Fig 5 Gross appearance of tumor exhibiting firm tan white tissue with fibrous consistency on the cut surface

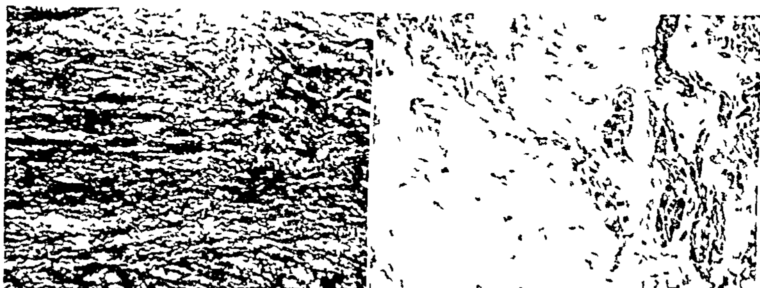


Fig 6 Left and Right Microscopic appearance Left Tumor border on left with interspersed bundles of myocardial tissue (Trichrome Original magnification ×136) Right Abundant elastic tissue throughout the tumor as demonstrated by special stain. (VVG Original magnification ×136)

tramural ventricular neoplasms located in the free wall of the left ventricle might be expected to produce alterations in the cardiac contour In the case reported here a bulge in the apical region correlated with the tumor location Similar findings have been noted by other observers[15,17] as well as the presence of calcifications in the tumor area [1,4,18]

In summary in the event of episodes of ventricular tachycardia in a child especially in the presence of an abnormal chest film the diagnosis of a ventricular tumor should be strongly considered Cardiac catheterization and angiography are necessary to adequately evaluate this possibility and provide an early diagnosis for a histologically benign lesion that may eventually have fatal consequences Surgical removal and disappearance of the arrhythmia may be possible as illustrated by this case

The authors are indebted to Avron Maletzky M D Seattle Wash who supplied the preoperative electrocardiogram

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was tenderness over the right hypochondrium It was possible to palpate a separate mass in the upper abdomen She was discharged from the hospital just before Christmas 1972

She attended as an out patient until her final admission on June 20 1973 Throughout this time she maintained her weight at about 54 kilograms her height being 5 feet (1 M 52 cm) although she was still having diarrhea abdominal pain and swelling of the ankles She had noticed a flickering in the neck A large mass could be palpated in the epigastric region

In June she complained of severe flushing of the face which had been worse for three months and left her with blemishes on the skin of her face and forearms She had paroxysmal nocturnal dyspnea on most nights and had frequent watery diarrhea She also had pain in her left loin On examination she was flushed and had pitting edema of the legs up to the knees The systemic blood pressure was 110/95 mm Hg with a radial pulse rate of 72 per minute in sinus rhythm There was obvious pulsation of the jugular veins She had a tender hepatomegaly a tender mass was palpable in the epigastrium There was a systolic murmur at the left sternal edge On June 26 at 5 30 A M. she had a severe attack of pain in the left side of the chest which radiated into the left shoulder and arm for several hours and she vomited frequently There was no associated calf tenderness She continued to feel very ill on the following days with frequent attacks of pain in the chest and she was sweaty and flushed On July 3 she complained that her hands and feet were cold and blue She died on July 7 1973

PROFESSOR WHITFIELD The important features in this case are that this woman had her appendix removed in 1964 and that subsequently she began to have pain in the right side of her abdomen associated with diarrhea and the passing of blood She had been losing weight and a mass was palpable in the right iliac fossa This mass could have been one of six lesions and three of these can be immediately excluded It might have been a swab left behind following her appendectomy but I am sure that that sort of event never occurs in Liverpool! The mass might have been a residual appendix abscess but this is really out of the question because the second operation would have cured this completely It might have been ileocecal tuberculosis but antituberculous therapy would have prevented the chronic illness from which she subsequently died She may have had a carcinoma of the cecum or ascending colon she may have had Crohn s disease The sixth possibility is that she may have had a carcinoid tumor A diagnosis of carcinoma is most unlikely because when the appendectomy was carried out such a lesion would have been noticed. The subsequent course of the disease is very much more like carcinoid than Crohn s disease

Carcinoid tumors occur most commonly in the appendix and small ones may be found in about one in every two hundred appendectomy specimens These tumors although malignant are slowly growing and derived from the Kultschitzky cells of the intestinal epithelium They are yellow in color and consist of epithelial cells in a fibrous stroma The intracytoplasmic granules in these cells give both an argentaffin and a chromaffin reaction and hence sometimes these tumors are called argentaffinomas. While carcinoid tumors are most frequent in the appendix they rarely give rise to the carcinoid syndrome when originating at this site However carcinoid tumors are commonly multicentric so that in this case it is possible that the patient had one in her appendix and a second one elsewhere in the gastrointestinal canal This tumor may have been too small to have been noticed at the first operation and may have escaped detection on radiography Perhaps it was present in the ileum or jejunum Less commonly the rectum cecum and colon might have been involved. Almost certainly this second carcinoid tumor produced the mass that was felt in 1965 although it seems unlikely that this palpable mass was entirely due to tumor tissue It is much more likely to have been due to a mass of fibrosis which is characteristically induced by such tumors I think that the operation that is described in the clinical summary was almost certainly a right hemicolectomy to remove this tumor The febrile illness which this patient experienced in June 1968 was probably an intercurrent and unimportant upper respiratory infection I interpret her symptoms of May 1972 as being due to a right sided diaphragmatic pleurisy and I believe that this was secondary to metastases of the carcinoid tumor in the liver It is conceivable that there were also secondary deposits in the lung but this is much less likely I note with interest that at this stage she had pulsation of the liver and of the jugular vein

Clinical pathologic conference

A G W Whitfield M D Ph D F R C P
A H Cruickshank, M D, Ph D, F R C Path
P J Dixon, M B, Ch B, M R C P
Donald Heath, M D Ph D, F R C P, F R C Path
Liverpool, England

DR DIXON The patient was admitted to the hospital on March 6 1965 at the age of 47 years She had had pain in the right iliac fossa for one month This pain was said to be intermittent and to last for hours It was not related to food and was not relieved by alkalies She had lost 14 pounds in weight in one month Three weeks before admission she had diarrhea for three days and on one occasion passed bright red blood On examination she was obese Her radial pulse rate was 70 per minute and was in sinus rhythm Her systemic blood pressure was 100/60 mm Hg The heart sounds were normal No abnormal signs were detected in the chest A tender smooth rounded mass was felt in the right loin This was situated just above an appendectomy scar (the appendix having been removed in 1964) An operation was carried out on March 11, 1965

On June 5 1968 she was readmitted following a bout of sickness and vomiting She had experienced aches and pains all over her body and had a slight cough On examination she was febrile (101° F) No fresh abnormal physical signs were elicited

She was readmitted to the hospital at 4 15 A M on May 5 1972, from the Casualty Department She had severe pain in the right hypochondrium which radiated into the back the right shoulder and neck The pain was described as being sharp and worse on inspiration and coughing It had been present for one week but had grown worse on the night of admission She had experienced a tight central chest pain on walking up hills for some weeks this was associated with breathlessness Her heart missed a beat often There was no history of hemoptysis or rheumatic fever

From the Medical School University of Liverpool Liverpool England.
Received for publication April 4 1974
Reprint requests Professor Donald Heath Department of Pathology Medical School University of Liverpool Liverpool England

On examination she looked ill, anemic and had koilonychia The radial pulse rate was 100 per minute with occasional extrasystoles The systemic blood pressure was 140/100 mm Hg There was no pitting edema of the ankles or sacral pad The apex beat was poorly localized The heart sounds were described as soft and a systolic murmur was heard at the base A sound described as a rub was heard at the lower left sternal edge Engorgement and pulsation of the jugular veins was found to extend some 10 cm above the clavicle There was a tender pulsating mass beneath the right costal margin Breathing was short and shallow and scattered wheezes were heard She improved with treatment and was discharged from the hospital at the beginning of June 1972

On August 15, 1972 she was readmitted to the hospital on account of a rash on the legs with edema She was discharged improved at the beginning of September 1972, and attended as an out patient until November 14 1972 when she was readmitted She said she was having attacks of facial flushing lasting a few minutes There were bouts of dizziness with loose watery stools sometimes containing slime and bright red blood Chest pain on exertion radiating into the left arm had become troublesome but eased on resting It was associated with breathlessness on exertion She had swelling of the ankles Her appetite was poor, she had lost ten pounds in weight, and was having feelings of sickness and pain one hour after eating

On examination she looked pale and ill There was a pronounced pulsation of the jugular veins in the neck which could be seen to the level of the angle of the jaw Her systemic blood pressure was 120/75 mm Hg There was some pitting edema of the ankles and sacral pad A systolic murmur was heard at the left sternal edge The edge of the liver could be felt to be pulsatile and there

of haustration but the small intestine appears to me to be normal I should think this barium enema could be classed as normal with no evidence of any primary lesion of the small or large bowel

DR ROBERTSON Perhaps one could point out that the film is not normal in that a right hemicolectomy has clearly been carried out in the past.

PROFESSOR WHITFIELD Yes I did not mention that although you will recall that I suggested previously that this lady had a right hemicolectomy for resection of a carcinoid tumor on March 11 1965

In December 1972 we find that a separate mass was palpable in the upper abdomen and I would imagine that this is a large secondary deposit in the liver or possibly a mass of lymph nodes with metastases into the mesentery This mass may have produced some of the deformity of the greater curve of the pyloric antrum which we have already noted on the barium meal

On her final admission she was found to have telangiectasia on her face and forearms commonly found in this syndrome She was also having paroxysmal nocturnal dyspnea which resulted from either bronchospasm or cardiac asthma The final severe attack of pain in the left side of the chest could have been pulmonary embolism or it could even have been myocardial infarction Chest radiographs or ECGs at this time would be very helpful

PROFESSOR HEATH Here is a radiograph of the chest taken on June 21 1973 (Fig 1)



Fig 1 Radiograph of chest taken on June 21 1973

PROFESSOR WHITFIELD This shows cardiac enlargement but there is no pulmonary edema to suggest left ventricular failure This suggests to me that this final dyspnea was largely due to bronchial constriction

PROFESSOR HEATH Here is an ECG carried out on June 26 1973 (Fig 2)

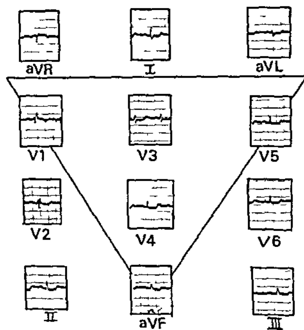


Fig 2 Electrocardiogram taken on June 26 1973

PROFESSOR WHITFIELD This shows some ST depression in Leads I II and III There are corresponding changes in Leads aV_R aV_L and aV_F. There is evidence of right bundle branch block and this would fit in with pulmonary embolism and with right sided valvular lesions associated with myocardial fibrosis

PROFESSOR HEATH The serum alanine aminotransferase levels were raised. In the laboratory in question the normal range is 5 to 25 mIU per milliliter whereas on May 5 1972 the level was 39 and on Oct 25 1972 it was 65 What do you think about that?

PROFESSOR WHITFIELD I would accept this raised level of transaminases as merely indicative of liver damage nature unspecified

PROFESSOR HEATH Supposing I allowed you to have one test to confirm your diagnosis which one would you choose?

PROFESSOR WHITFIELD I should choose to see the total 5 hydroxytryptamine indole excretion in the urine over a period of 24 hours Normally

which indicate tricuspid incompetence This complication of valvular heart disease is very characteristic of carcinoid tumors and has the same basis of fibrosis to which I have already referred This fibrosis produces tricuspid incompetence and pulmonary stenosis These cardiac complications only occur in the presence of hepatic metastases The description of the cardiac murmur is not adequate to allow me to say whether this was produced by the incompetent tricuspid valve or the stenosed pulmonary valve The friction rub which is reported may have been pleurisy but may have been secondary to constrictive pericarditis again due to the fibrosing process set up by the tumor The bronchospasm which she was experiencing at this time is also typical of the carcinoid syndrome probably related to excessive secretion by the tumor of 5 6 hydroxytryptamine All of us have small amounts of serotonin in our blood produced by the Kultschitzky cells, but in the carcinoid syndrome this level is greatly increased It is much easier to assess the output of 5 6 hydroxytryptamine by an estimation of its degradation product, namely the total 5 hydroxyindole excretion in urine over 24 hours which should not normally exceed 10 mg

PROFESSOR HEATH Here is the chest radiograph taken on May 5, 1972

PROFESSOR WHITFIELD This shows some cardiac enlargement which appears to be involving the left ventricle but that would be difficult to fit in with my hypothesis There is no radiographic evidence of left ventricular failure People with the carcinoid syndrome do not usually have valve defects on the left side of the heart unless secretions of the tumor drain into the left atrium It is the tricuspid and pulmonary valves which become involved If however there was an atrial septal defect with hepatic metastases of an ileal carcinoid or a primary bronchial carcinoid then one could have left sided valvular lesions

It is clear from this clinical story that this patient was experiencing anginal pain on exercise The combination of tricuspid incompetence and pulmonary stenosis would lead to a poor blood supply to her left ventricle with a poor cardiac output Furthermore it is clear that she was anemic with koilonychia These are adequate causes for her to have myocardial ischemic pain without coronary artery disease The electrocardiogram taken on May 5, 1972, shows a rate of 84 per minute in sinus rhythm and it is of low voltage, but is otherwise normal

PROFESSOR HEATH The low voltage tracing bothered the clinicians at the time that this patient was seen on the ward They asked for an estimation of the serum protein bound iodine and this proved to be 5 7 μg per 100 ml, the normal range in this laboratory being 4 to 8 μg per 100 ml

PROFESSOR WHITFIELD This is a normal level and indicates that the patient did not have myxedema The case description of course does not indicate the clinical picture of myxedema

DR HUDGINS Would not the low voltage electrocardiogram (ECG) be consistent with pericarditis produced by the carcinoid syndrome?

PROFESSOR WHITFIELD Yes it would When this patient was readmitted after a short period of improvement she had developed two new symptoms One of these was facial flushing which is highly characteristic of this syndrome It affects predominantly the face and neck and lasts for a few minutes In the past this flushing has been attributed to the high level of serotonin in the blood but recent evidence suggests that other substances are more likely to be responsible These include bradykinin, kallikrein prostaglandins and histamine The flushing is provoked by hot drinks, meals of cheese or salty foods excitement, alcohol or bowel actions The second symptom was diarrhea, also very characteristic of this syndrome This is also believed to follow serotonin secretion and is commonly associated with malabsorption and pellagra type rashes Probably this was the sort of rash she had on her legs

PROFESSOR HEATH Would you care to see the barium meal carried out on Nov 17 1972?

PROFESSOR WHITFIELD I think it would be worthwhile looking at that since we know she had blood in her bowel movements at that time and it might have been due to another primary lesion in the gut rather than being an association of the diarrhea caused by the carcinoid syndrome Well there is a deformity of the pyloric antrum and there is some deformity of the duodenal cap which I suspect is due to previous ulceration Peptic ulceration of this type is commonly associated with the carcinoid syndrome

PROFESSOR HEATH Here is a barium enema carried out in the same month

PROFESSOR WHITFIELD There is a certain lack

the pulmonary valve were shrunken distorted, and thickened to produce narrowing of the valve ring to a diameter of 0 7 cm (Fig 4) The cusps also appear to have been incompetent and were so shrunken as to have obliterated the sinuses of Valsalva except for a small diverticulum like recess 0 3 cm in diameter on the posterior aspect There was pronounced thickening of the cusps of the tricuspid valve each being 0 3 cm thick and the chordae tendineae were thickened and fibrotic This valve appeared to be severely incompetent (Fig 4) The muscle of the right ventricle was extensively replaced by fibrous tissue in its posterior and inferior portions but the dilated conus was almost free from fibrosis (Fig 5) The left side of the heart including the mitral and aortic valves was normal The coronary arteries were free from atheroma Both atria had opacity of the endocardium and the right atrium was extensively replaced by fibrous tissue and felt rigid The aorta throughout its length was free from atheroma

The stomach was normal and no pre pyloric ulcer was found. The small intestine was normal apart from an old anastomosis between the ileum and the ascending colon The anastomosis was situated in the right iliac fossa It was surrounded by omental adhesions and there were adhesions between the anatomosis and the scar in the abdominal wall Beyond the anastomosis the colon was normal

The liver was enlarged and a pedunculated almost spherical mass 9 cm in diameter was attached to the anterior margin of the left lobe just to the left of the falciform ligament (Fig 6) Slightly smaller masses were present in the right lobe of the liver near its anterior margin (Fig 6) They encroached upon the gall bladder which was distorted by a fibrous stricture A number of small rounded deposits 1 to 3 cm in diameter were scattered throughout the liver in which there was also marked chronic venous congestion The cut surfaces of the masses of tumor in the liver were a pale cream color and very vascular there was central hemorrhage in the pedunculated mass attached to the left lobe of the liver Small lymph nodes containing tumor tissue similar to that in the liver were attached to the upper border of the pancreas near its head. A rounded nodule of secondary tumor 1 cm. in diameter was embedded in the middle of the body of the pancreas



Fig 6 A coronal section of the liver in which hemorrhagic metastatic carcinoid tissue is attached by a pedicle to the left lobe (arrow) Two other metastatic carcinoid tumors, m lie under the capsule of the right lobe (×1/3)

The spleen was a little enlarged and had a large area of infarction in its upper half with overlying adhesions The kidneys ureters urinary bladder and ovaries were normal but retroperitoneal fibrosis in the pelvic cavity was marked especially around the iliac vessels The pituitary thyroid, and adrenal glands were normal

There was no evidence of pulmonary thromboembolism

The findings at necropsy confirm the combination of tricuspid incompetence and pulmonary stenosis which Professor Whitfield has deduced were present in this patient The myocardial fibrosis of the right ventricle may account for the right bundle branch block noted in the later ECGs There was no disease of the coronary arteries to account for the history of anginal pain and it seems likely that this had been produced in the manner described previously by our clinical speaker There was no pulmonary thromboembolism to account for the pain in the left side of the chest and I attribute this pain to the large infarct of the spleen I could not find a source for the embolus that caused this infarct Similarly I was unable to find an anatomic cause of death in this patient

In summary the features at necropsy were those to be expected in the carcinoid syndrome hepatic metastases from an intestinal carcinoid associated with cardiac disease composing tricuspid incompetence and pulmonary stenosis The histology of the original carcinoid tumor was classical in sections stained with hematoxylin



Fig 3 The microscopic appearance of the primary alimentary tumor in which darkly staining clumps of carcinoid tumor cells are spreading beneath a mucous membrane that seems to be colonic (Hematoxylin and eosin × 60)



Fig 4 The ventricular aspect of the incompetent fibrosed and thickened tricuspid valve and the stenotic pulmonary valve (arrow) with the adjacent endocardial fibrosis Natural size

this is less than 10 mg, as I have said previously

PROFESSOR HEATH On May 10 1972 it was 120 mg on Nov 15, 1972 it was 220 mg and on June 6 1973, it was 303 mg

PROFESSOR WHITFIELD These results confirm that my diagnosis is correct Of course one has to accept the fact that this test can be upset if the patient has been eating large quantities of bananas which contain a great deal of serotonin There are 4 mg of serotonin in one banana

PROFESSOR HEATH Dr Dixon had this patient been eating large numbers of bananas?

DR DIXON Not to my knowledge



Fig 5 The wall of the right ventricle with its thick layer of darkly staining subendocardial fibrous tissue (Millers Elastic Stain with Van Gieson Counterstain × 4 4)

PROFESSOR HEATH Armed with this assurance we can now ask Dr Cruickshank what he found at necropsy

DR CRUICKSHANK The original hemicolectomy specimen received at another hospital in 1965 was said to have included a carcinoid tumor 2 by 1 cm on its mucosal surface and a smaller nodule on its peritoneal surface I have examined the relevant sections and they contain a characteristic carcinoid tumor in which there is infiltration of the underlying muscle coat of the gut by clumps and islands of cells showing intracytoplasmic granules that give a typical positive staining reaction with silver and diazo techniques The overlying intestinal epithelium in the sections I have examined indicates that the carcinoid tumor arose from the colon (Fig 3)

At necropsy there was heart disease of the type now well known to be associated with the carcinoid syndrome The heart was enlarged and this enlargement especially involved the right ventricle and its conus There was pulmonary stenosis and tricuspid incompetence The cusps of

cinoid syndrome but I have read of them and should these cause any elevation of left atrial pressure they would lead to pulmonary arterial hypertension

DR. CRUICKSHANK Would you not expect that the pulmonary stenosis likely to occur in this syndrome would exert a protective effect on the pulmonary circulation?

PROFESSOR HEATH There is no doubt that this is a rare syndrome In the new British Health Service each area will comprise about half a million people and statistically one would anticipate two to four cases of the carcinoid syndrome in such a population every decade However rare as the condition is it gives us a fascinating insight into the important system of argentaffin and argyrophilic cells in the body which appears to have the capacity for secreting a wide range of humoral substances

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and eosin, silver and the diazo method The patient had been dead for 48 hours before permission to carry out a necropsy could be obtained and the silver and diazo methods were then, predictably disappointing However sections stained with hematoxylin and eosin were typical moreover the lead hematoxylin method gave a positive result and this is a histologic test for APUD cells i e those containing polypeptide hormones and related substances The term 'APUD is derived from the initial letters of certain biochemical characteristics of these cells such as amine precursor uptake and decarboxylation

PROFESSOR HEATH This peculiar combination of a pelvic tumor with tricuspid and pulmonary stenosis forms a highly distinctive syndrome and appears to have been first reported in a patient in 1930 by Dr Maurice Cassidy at the Royal Society of Medicine[1] At that time, the carcinoid syndrome had not been recognized but it is so characteristic that we can look back and identify this case for what it was Since that time over the past forty years, the widespread and important nature of these argentaffin and argyrophilic cells throughout the body has become apparent If there is a message from this meeting for medical students it is that medical science and knowledge are gradually evolving all the time We have seen this afternoon how argentaffin cells in carcinoid metastases in the liver may secrete serotonin and kallikrein and give rise to this peculiar syndrome It is however becoming increasingly clear that throughout the body there is a whole system of argentaffin and argyrophilic cells Thus Feyrter cells in the bronchial tree and chief cells in the carotid body are both argyrophilic These are varieties of APUD cells which are said to secrete polypeptide hormones It is only recently that it has been discovered that the argyrophilic cells of the thyroid the so called C cells secrete calcitonin Is it possible that the argyrophil cells in the bronchial tree secrete a hormone? The carotid body is the classical chemoreceptor but does it also secrete a hormone? So this consideration of the carcinoid syndrome has wide implications

We are honored to have with us this afternoon one of my predecessors who is an international authority on endocrine pathology and gave his name to 'Sheehan's syndrome" Professor Sheehan would you regard the bronchial tree as an endocrine organ?

PROFESSOR SHEEHAN There is no doubt that it has the capacity for producing not only serotonin but a whole range of other hormones

DR DAVIS I would agree that the bronchial tree might well prove to be one of the most versatile producers of endocrines in the body It is interesting to speculate as to what their normal physiologic functions are as well as to observe the clinical syndromes to which their hypersecretion, on occasion, give rise

DR ROBERTSON It is strange that the peculiar type of flushing that this lady showed to such a degree and the associated telangiectasia seem to occur only on the face in this disease Presumably, serotonin has the same vasomotor effect on all blood capillaries in the skin

PROFESSOR WHITFIELD I agree Four different types of flushing have been described and attempts have been made to identify the different factors that produce them However I am still confused as to the pharmacologic basis for the various forms With regard to the treatment of flushing partial hepatectomy with removal of actively secreting metastases may give a patient several years of comparatively comfortable life It has to be borne in mind that the primary carcinoid tumor is slowly growing so patients may survive from five to twenty years.

DR KAY Is it possible to treat this syndrome pharmacologically in any way by some substance which would inhibit the synthesis of these chemicals or possibly by antagonizing their action?

PROFESSOR WHITFIELD Well efforts have been made to treat certain aspects of the syndrome The diarrhea can be controlled to some extent by methysergide and also by parachlorophenyl alanine but of course methysergide can produce retroperitoneal fibrosis

DR KAY Does pulmonary hypertension ever occur in association with the carcinoid syndrome? The metastases secrete prostaglandins and 5 hydroxytryptamine which have been shown in some animal species to have vasoconstrictor activity For example prostaglandin $F2\alpha$ is a potent pulmonary vasoconstrictor

PROFESSOR WHITFIELD I cannot recall having seen any reports of pulmonary hypertension complicating the carcinoid syndrome I have never seen left sided valvular lesions in the car

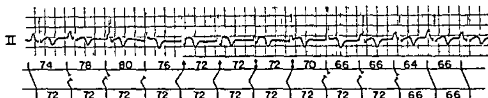


Fig 1 Accelerated A V junctional rhythm without A V block causing in a sinus arrhythmia transient complete (upright arrow) or partial (opposing arrows) retrograde activation of the atria or A V dissociation All numbers within the conventional ladder diagrams and electrocardiograms in this and subsequent figures indicate hundredths of a second (unless indicated otherwise)

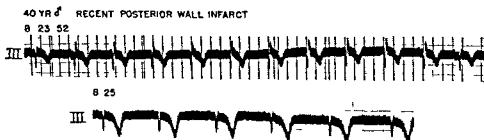


Fig 2 Transient acceleration of A V junctional impulse formation (without A V block) causing temporary isorhythmic A V dissociation. (From Pick and Dominguez. Nonparoxysmal A V nodal tachycardia Circulation 16 1022 1957 Reproduced by permission of the American Heart Association)

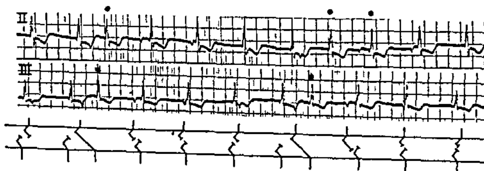


Fig 3 Acceleration of two A V junctional pacemakers with retrograde A V block causing incomplete dissociation within the A V junction Ventricular captures by the upper junctional pacemaker are indicated by black dots.

block can be seen in a similar case illustrated in Fig 2 In the record of Aug 23 only the first and the last beats are conducted sinus impulses In between is either an isorhythmic A V dissociation [11] as the sinus rate has slowed *transiently* to equal the accelerated junctional escape rate of 75 or the atria may be captured in a *retrograde* manner by junctional impulses [12,13] Two days later escape beats no longer *occur* although the sinus rate is reduced to 54 The *restriction* of abnormality to junctional automaticity is revealed by the normal A V conduction time of 0 14 sec. on both occasions. Slight aberration of intraventricular conduction in the junctional beats consisting in a larger R wave facilitates their distinction from conducted sinus beats This could be due to partial depolarization of part of the ventricular Purkinje tissue during an enhanced phase 4 in cells of the A V junction[14] or to the use of some preferential path of junctional impulses on their way to the ventricles [15,16]

Accelerated functional impulse *formation with* unidirectional block The record illustrated in Fig 3 was obtained in a 64 year old man with chronic cor pulmonale who had received excessive amounts of a digitalis glycoside Throughout Leads

Fundamentals of clinical cardiology

The dual function of the A-V junction

Alfred Pick
Richard Langendorf
Chicago Ill.

The part of the specialized conduction system connecting the atria with the ventricles, named, according to present accepted terminology, the A V junction,[1] is composed of the following anatomically and histologically discernible tissues (1) the approach fibers to the A V node, (2) the A V node (3) the penetrating, and (4) the nonpenetrating nonbranching portions of the A V bundle Electrophysiologically, four types of specific fibers have been identified in this region [2,3] (1) the N fibers within the A V node (2) Purkinje like fibers in the subdivisions of the common A V bundle and (3) and (4) transitional A N and N H fibers in nodal parts adjacent to the atria and to the common bundle of His These latter fibers differ with regard to the shape, size, and duration of their action potentials and in their function Cells from the N region regulate normal and abnormal impulse transmission from the atria to the ventricles, and vice versa, but lack automaticity, that is, the ability to generate impulses [4-6] Viewed teleologically, their function appears to be protection of the ventricles from too rapid stimulation In contrast cells of the A N and N H regions and of the His bundle can in addition, produce impulses and thereby protect the ventricles from too slow beating or asystole in the event that the primary pacemaker fails or transmission of impulses to the ventricles is prevented

In human pathology and in clinical electrocardiograms this division of functional properties of A V junctional cells can be appreciated when their derangement develops independently or in succession Abnormal impulse *formation* is characterized by its gradual acceleration, a non paroxysmal junctional tachycardia [7] or by failure of junctional escapes to occur when expected [8,9] Abnormal impulse *transmission* is recognized by slowing, or partial or complete block of A V or V A conduction A combination or separation of these abnormalities is particularly seen with excessive digitalis effects, in recent diaphragmatic infarction in acute rheumatic fever following surgical interventions near or on the cardiac septa,[9] and in the form of the tachycardia bradycardia syndrome [10] Eight representative clinical observations were selected for demonstration

Acceleration of junctional impulse formation without block Fig 1 shows the electrocardiogram (Lead II) of a 54 year old woman in an acute stage of diaphragmatic myocardial infarction During a sinus arrhythmia an accelerated subsidiary pacemaker in the A V junction escapes with a cycle length of 0 72 sec and continues to escape as long as the length of the sinus cycle exceeds 0 74 sec After a short period of A V dissociation, two retrograde junctional impulses succeed in complete capture of the atria indicated in the diagram by the upright arrow heads Thereafter sinus impulses gradually accelerate to collide with junctional impulses at first in the atria, causing two atrial fusion beats then within the A V junction before regaining command of the entire heart in the last two beats During all this time antegrade as well as retrograde conduction across the A V junction is not impaired and this allows for the prompt transition of an isorhythmic A V dissociation into retrograde capture of the atria or antegrade capture of the ventricles depending on the immediate sinus rate

The transient nature of such a nonparoxysmal junctional tachycardia in the absence of A V

From the Cardiovascular Institute Department of Medicine Michael Reese Medical Center Chicago

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Reprint requests Dr Alfred Pick Michael Reese Medical Center 29 St. and Ellis Ave Chicago Ill 60616

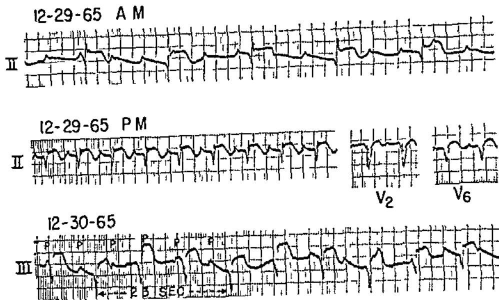


Fig 6 Complete A V dissociation caused by rapid A V junctional impulse formation with different ventricular rates due to varying antegrade exit block (see Table I and text)

tivity is best appreciated when the two develop and disappear in succession Fig 4 shows four consecutive records of a 7 year old girl in the course of acute rheumatic carditis. On Aug 26 the rate of a junctional pacemaker 136 per minute exceeds that of a sinus tachycardia of 125 resulting in incomplete A V dissociation The symbols on top indicate several successive captures of the ventricles by sinus impulses some with a normal P R of 0 18 sec Prolongation of A V conduction in the others is caused by physiologic refractoriness below the site of the junctional pacemaker resulting in the rare phenomenon of delayed captures [7] Hence on this day antegrade impulse conduction was not abnormal However the middle record taken the next day shows that the A V dissociation became complete without any change in the rate of the atria or ventricles Thus in addition to the abnormally fast impulse generation in the A V junction development of some depression of antegrade impulse conduction must be postulated to account for the absence of ventricular captures Subsequently the sequence of disturbance of the function was reversed On Aug 29 with a slower sinus rate of 96 junctional beats were no longer present, while a first degree A V block with a P R interval of 0 28 sec became evident to disappear only six days later at the same sinus rate of 96

This sequence of the dual manifestation of functional pathology in the A V junction is usually different in cases of recent diaphragmatic myocardial infarction in that A V block of various degrees tends to precede the onset of a nonparoxysmal junctional tachycardia In the example shown in Fig 5 the first electrocardiogram on Jan 13 reveals complete A V dissociation due to an advanced probably complete A V block with a long junctional escape cycle of 1 46 sec giving a regular ventricular rate of 41 In a record taken two days later obtained without any therapeutic intervention the A V block is reduced to a second degree of Mobitz type I with conduction ratios of 3 2 The two conducted beats alternate with two junctional escapes the cycle of which measures only 0 94 sec compared to 1 46 sec (see the first record) This indicates acceleration of junctional impulse formation to 65 while the sinus rate remained 83 On Jan 17 only a first degree A V block with a P R of 0 24 sec was recorded, and no escapes were noted although the uneven sinus rate at times dropped to 56 per minute Here then a transient period of a nonparoxysmal junctional tachycardia intervened during slow regression of A V block Whether under such circumstances A V dissociation develops, whether it is complete or incomplete and the length of its duration will depend on three variables (1) the degree of block in

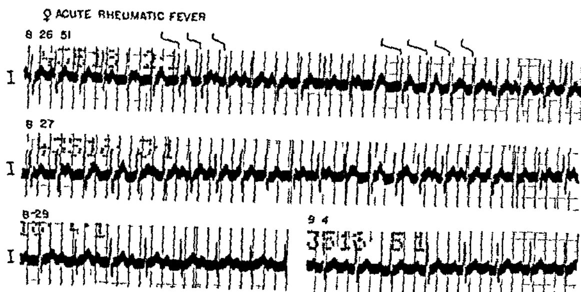


Fig 4 Transient acceleration of A V junctional impulse formation preceding development of A V block The symbols above the top panel indicate ventricular capture at variable P R intervals (From Pick and Dominguez Nonparoxysmal A V nodal tachycardia Circulation 16 1022 1957 Reproduced by permission of the American Heart Association)

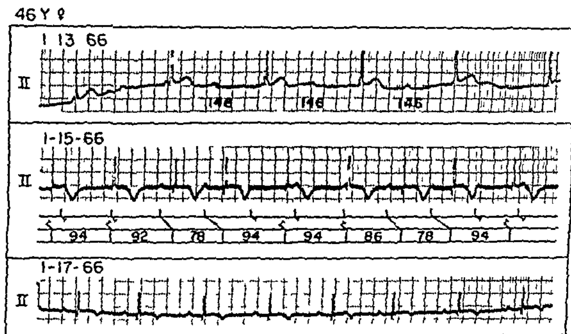


Fig 5 Transient A V block preceding acceleration of A V junctional impulse formation

II and III, P waves of retrograde shape can be spaced at a regular rate of 65 Ventricular beats of supraventricular contour are faster 71 per minute and regular, with five exceptions labeled by dots Only these beats can be linked to P waves at P R intervals that vary inversely with R P distances Elsewhere, the atrial and ven tricular actions are independent Thus in complete A V dissociation is present that is in duced by simultaneous but unequal acceleration of two subsidiary junctional pacemakers [9, 17, 18] The slower one in the upper A V junction main tains control of the atria and succeeds on five oc casions in capturing the ventricles constituting evidence that outside the normal refractory period of the A V junction antegrade A V con duction is not impaired Conversely all faster im pulses originating in the lower A V junction are prevented by a retrograde block from traversing the upper junction to reach the atria They pre dominate in the activation of the ventricles with the exception of five premature captures by prox imal junctional impulses

The sequence of dissociation of functional dis orders of the A V junction *Dissociation of abnor malities in junctional automaticity and conduc*

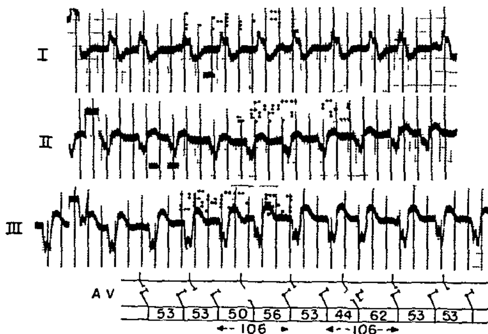


Fig 7 Incomplete A V dissociation due to parasystolic accelerated impulse formation in the A V junction (in left bundle branch block) The dotted semicircles in the diagram indicate bypassing of the area of junctional impulse formation by conducted sinus impulses

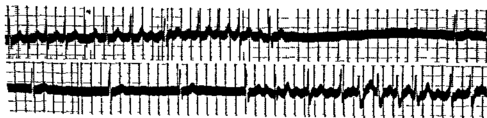


Fig 8 Two paroxysms of atrial fibrillation with rapid ventricular response with a period of complete cardiac ar rest and of a warming up junctional escaping pacemaker in between (an example of the tachycardia bradycar dia syndrom) Continuous Lead II—Last QRS of upper strip reproduced as first QRS of lower strip (From Katz and Pick Clinical Electrocardiography Part I The Arrhythmias Philadelphia 1956 Lea and Febiger Reproduced by permission)

can take place without any block or in conjunc tion with various degrees and types of abnormal conduction Another example of separation of functional abnormalities of the A V junction is *depression* of impulse formation without any im pairment of conduction, as is seen in many cases of the tachycardia bradycardia syndrome[10] Fig 8 shows one of many similar episodes in a 66 year old woman with ischemic heart disea e At the left of the upper portion of the continuous record is seen the sudden spontaneous end of a paroxysm of atrial fibrillation with a rapid ventricular response of 120 to 150 per minute which indicates a normal state of A V conduc tivity In contrast marked sluggishness of sub sidiary impulse formation in the A V junction is evident in the long subsequent total asystole It takes in the absence of any atrial activity almost four seconds before an A V junctional escape occurs followed by three others (lower strip) with gradual shortening of their cycle to 1 62 and 1 38 sec (indicating warming up of the subsidiary pacemaker) After the fourth escape a new paroxysm of atrial fibrillation sets in again with a fast ventricular response and transient repetitive aberrant ventricular conduc tion after a short cycle had followed a longer one[21]

Table I Atrial and ventricular cycles (in hundredths of a second) in Fig 6

	12 29		*12 30*
	A M	*P M*	
Atrial rate	115	100 104	104
Ventricular rate	43	104	80
Ventricular cycle	140 (7 × 20)	57 (3 × 19)	76 (4 × 19)

antegrade and retrograde direction (2) the extent of acceleration of junctional automaticity, and (3) the sinus rate [19]

Accelerated junctional impulse formation with exit block A slow ventricular rate in the electrocardiogram may not reflect the actual rapid discharge of impulses by the A V junction as illustrated by Fig 6 and Table I Fig 6 shows three consecutive records of a 72 year old woman admitted for a second myocardial infarction In the first panel, atrial and ventricular actions are completely dissociated due to a high degree of A V block with a very slow junctional escape rate The middle record taken several hours after the top record, suggests at first glance a sinus tachycardia with a first degree A V block However a variable P R distance without changes of the ventricular rate illustrated in the two chest leads V_2 and V_6 reveals the persistence of A V dissociation The bottom record taken the next morning the day the patient died still shows complete A V dissociation with a ventricular rate intermediate between those of the previous two electrocardiograms (The distance of 2 3 sec between four ventricular beats corresponds to one respiratory cycle)

The atrial and ventricular rates of the three records are listed in Table I Only an insignificant change occurs in the atrial rate in contrast to that of the ventricles Expressed as ventricular cycle length, it can be noted that the three values of 140, 57, and 76 are multiples of a common denominator of about 20 This fact suggests that throughout the entire observation a regular junctional pacemaker kept firing at a very rapid rate of about 300 with a variable exit block At first, only every seventh impulse was effective causing the slow regular ventricular rate of 43 It reached its maximum of 104 when the exit ratio changed to 3 1, and slowed again to 80 when only every fourth impulse reached the ventricles Thus, in this case the functional derangement of the A V junction was manifested by the combination of continuous rapid impulse formation with two regions of block a proximal complete one and a distal variable one of second degree The precise numerical relationship of short and long cycles suggests that this second degree block was of Mobitz type II and most likely localized in the bundle of His below the area of rapid impulse formation In agreement with this interpretation, autopsy revealed inclusion of the bundle of His in a fresh posteroseptal and atrial infarction, whereas the A V node itself was spared.[20]

Unidirectional protection block of an accelerated A V junction pacemaker (with incomplete A V dissociation) When a *unidirectional* block is located near the area of accelerated impulse formation within the A V junction it may protect the junctional pacemaker from invasion by other especially sinus impulses and a resulting A V dissociation may present as a junctional parasystole One rare example with a diagram of the mechanism, is shown in Fig 7 a record obtained in the course of digitalization in a 44 year old man with hypertensive heart disease and, probably cardiomyopathy As a result of acceleration of a subsidiary pacemaker without retrograde conduction to the atria an incomplete A V dissociation has developed, with several ventricular captures by sinus impulses occurring when appropriately timed within the ectopic cycles Since captures and automatic beats have the same contour a junctional origin of the tachycardia in the presence of left bundle branch block is assumed in the diagram although, admittedly, an accelerated pacemaker situated in specific fibers of the right bundle branch system can not be ruled out The diagram also shows that the distance of assumed junctional beats containing ventricular captures measures 1 06 sec precisely twice the regular ectopic cycle of 0 53 sec Therefore sinus impulses that succeeded in traversing the A V junction must have bypassed the site of the accelerated ectopic focus protected by a unidirectional entrance block—the hallmark of a parasystole

Depression of impulse formation without any block in the A V junction In the records shown thus far it was demonstrated that enhancement of impulse generation in A V junctional tissues

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Table II Manifestations of dissociation of functions of the A V junction in clinical electrocardiography

Mechanisms	*Result*
I Acceleration of impulse formation (in one or two junctional pacemakers)	
a Without any block	Junctional tachycardia with retrograde conduction to atria or isorhythmic A V dissociation
b With retrograde block	Incomplete A V dissociation with ventricular captures
c With retrograde and first or second degree antegrade block	*Incomplete or complete A V dissociation*
d With exit block	A V dissociation with slow ventricular rate
e *With unidirectional entrance block* (in addition to retrograde A V block)	A V junctional parasystole (with incomplete A V dissociation)
II Depression of impulse formation without any block in the A V junction.	Tachycardia bradycardia syndrome

Summary

The various electrocardiographic syndromes that develop as a consequence of abnormal dissociation of the two functions of the A V junction can be summarized as follows (Table II)

Acceleration of impulse formation in one or two pacemakers without any block in the A V junction leads either to junctional rhythm with retrograde activation of the atria, or to isorhythmic A V dissociation when associated with retrograde block the dissociation is incomplete with ventricular captures when first or second degree antegrade block develops in addition the captures tend to disappear and the A V dissociation to become complete An exit block of the junctional impulses may slow the manifest ventricular rate during the dissociation, and finally an additional protective entrance block around the junctional pacemaker results in junctional parasystole On the other hand *depression* of junctional impulse formation without A V block is one of the mechanisms responsible for the tachycardia bradycardia syndrome

The basis of such a functional separation of the two properties of A V junctional tissues appears to be a difference in structure and electrophysiologic behavior of cell elements that constitute the A V junction

Addendum

While this article was in press Rosenbaum and Assoc. (Circulation 49 818 1974) published a study on relationships between increased automaticity and depressed conduction in injured fascicles of the ventricular conduction system On occasion they observed a dissociation of the effects of injury upon automaticity and conduction similar to that described here for the A V junction As one of the explanations they offered differences in functional states of cell groups in the injured area

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the excitable regions of the AV node is slow enough, the impulse may enter the region in which conduction block occurred in a retrograde direction after its fibers have recovered excitability and return to re excite the atrium as a re entrant impulse or return extrasystole (Fig 5B) The antegrade conduction pathway with the shorter refractory period has been called the alpha pathway by Mendez and Moe while the retrograde pathway with the longer refractory period has been called the beta pathway [19]

In addition to returning to the atrium, the atrial impulse may also conduct in an antegrade direction to activate the His bundle and the ventricles (Fig 5B) The lower region of the AV node is not part of the re entrant pathway [19] Therefore, re entry of a premature atrial impulse can still occur in the absence of a ventricular response (a premature impulse which is not conducted to the ventricles can still return to re excite the atrium)

The relationship of the conduction velocity of the impulse through the cells in the antegrade pathway to the refractory period of the cells in both the retrograde pathway and the atrium is important for the same reasons described for the ventricular conducting system If the premature atrial impulse travels too rapidly through the antegrade pathway it may enter the retrograde pathway and return either to the region of conduction block or to the atrium before these areas have recovered excitability Thus a re entrant impulse or atrial echo will not occur

The mechanisms described for single re entry of atrial impulses in the AV node also can result in continuous re entry [19,20,21] If a re entrant impulse returns to the atrium at a time when the nodal fibers which it previously excited in the antegrade pathway have recovered excitability the impulse once again can enter the AV node and conduct around the circuit This can become a continuous process activating the atrium each time the impulse conducts around the re entrant loop The impulse can continue to conduct around the re entrant circuit in the upper and mid AV node while conduction from the mid to the lower nodal region shows variable degrees of block in which case sustained atrial tachycardia will occur in the presence of AV conduction block [20]

Re entry of a premature atrial impulse through the AV node presumably can occur in a normal heart Re entry of non premature sinus impulses in the AV node may require pathophysiological alterations in AV nodal function Disease processes may increase the disparity of refractoriness between different groups of nodal cells so that conduction of the sinus impulse blocks in one region of the node but not another

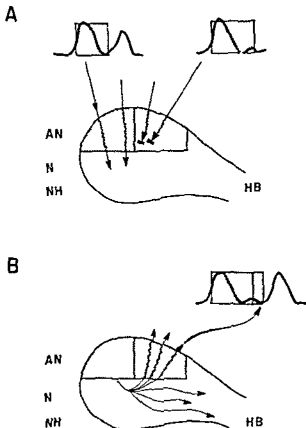


Fig 5 A and B Re entry of an atrial impulse in the AV node Both panels show diagrammatic representations of the AV node with the upper (AN) middle (N) and lower (NH) node indicated HB is the His bundle In A action potentials recorded from two regions of the upper node are shown at the top The action potential at the left has a shorter refractory period than the action potential at the right as indicated by the shaded area. Therefore when a premature atrial impulse enters the AV node (arrows) it may be able to excite the part of the upper node with the shorter refractory period but block in the region with the longer refractory period. This is also indicated in the action potential recordings at the top B shows the continuation of these events The impulse can return to excite the area of the node in which antegrade conduction block occurred and then re enter the atrium Action potentials recorded from the return nodal pathway are shown the first action potential results from conduction of the sinus impulse followed by low amplitude depolarization resulting from conduction block of the premature impulse followed by an action potential resulting from the return impulse

Electrophysiology and pharmacology of cardiac arrhythmias II Relationship of normal and abnormal electrical activity of cardiac fibers to the genesis of arrhythmias b Re-entry Section II

Andrew L Wit Ph D*
Michael R Rosen, M D*
Brian F Hoffman M D
New York N Y

III The slow response slow conduction and re entry in the AV and sinus nodes

Re entry within the sinus and AV nodes results from many of the same basic mechanisms which were described for re entry in the ventricular conducting system slow conduction and unidirectional block are essential The fibers of the sinus and AV nodes develop slow response action potentials[16] and conduction in them is slow Therefore, partial depolarization by disease is not necessary for re entry to occur Anatomically well defined re entrant pathways such as those which may occur in the peripheral ventricular specialized conducting system may or may not exist in the nodes The re entrant pathway probably results from functional differences between different groups of nodal cells

AV nodal re entry Refractoriness of AV nodal cells significantly outlasts complete repolarization so that nodal cells may be either completely refractory or partially refractory long after membrane potential has returned to its maximal diastolic value [17,18] In addition to this the refractory period of different nodal cells is highly variable Cells at the atrial end of the node (AN region) appear to constitute several populations with different refractory periods One group of cells has a refractory period which is significantly longer than that of the other (Fig 5) Under appropriate conditions this difference in refractoriness of the cells in the upper nodal region is important for the formation of a functional re entrant pathway [19] A sinus impulse which reaches the AV node long after recovery of excitability in both groups of cells will conduct through all these fibers to the His bundle Similarly an atrial premature impulse occurring late in the basic cycle length usually will propagate through all the fibers in the AV node since it reaches them after they have recovered excitability The disparity in refractoriness of upper nodal fibers becomes significant in determining conduction patterns for rapid irregular impulses or early premature atrial impulses As early premature atrial impulses conduct into the node they will begin to encounter refractory nodal tissue in the region where the effective refractory period of the cells is the longest (Fig 5A) Conduction of a premature impulse may therefore block in these areas of the upper AV node where the refractory period is the longest while still conducting through upper nodal fibers which have shorter refractory periods and have partly recovered excitability (Fig 5A) The region of conduction block in the fibers with the longer refractory period is an area of unidirectional block Therefore the differences in refractory periods of the two populations of cells functionally divide the AV node into two pathways for the conduction of early premature impulses If conduction of the premature impulse through

From the Department of Pharmacology College of Physicians and Surgeons Columbia University New York N Y

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Reprint requests to Dr Michael R. Rosen Department of Pharmacology College of Physicians and Surgeons 630 W 168th St New York, N Y 10032

Dr Wit and Dr Rosen are *Senior Investigators* of the New York Heart Association Dr Rosen is a Research Fellow of the John Polachek Foundation Dr Wit is a Career Scientist of the Irma T Hirschl Trust.

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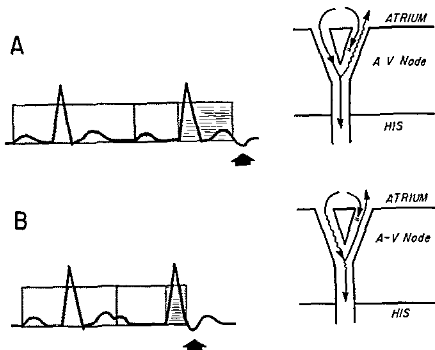


Fig 7 A and B Electrophysiological basis for reciprocal relationship between the P R interval of the impulse preceding the re entrant extrasystole and the R P interval of the return impulse Diagrammatic electrocardiographic tracings are at the left At the right are diagrams of the re entrant AV nodal pathway according to Mendez and Moe [19] with the upper AV node divided into an antegrade and retrograde pathway determined by the refractoriness of cells in each region (*see Fig 5*) In *A* the P P interval between the sinus impulse and the premature atrial impulse (diagonally shaded area) is relatively long and therefore the P R interval of the premature impulse is short (*stippled area*) This indicates that the premature impulse conducts relatively rapidly through the AV node in the antegrade pathway shown in the diagram to the right As a result the R P interval (horizontally shaded area) of the return extrasystole (indicated by arrow) is long because conduction in the retrograde pathway is slowed as indicated by the wavy line and arrow in the diagram at the right In *B* the P P interval between the sinus impulse and premature atrial impulse is shorter (*diagonally shaded area*) and therefore the P R interval of the premature impulse is long (*stippled area*) This indicates that the premature impulse conducts slowly through the AV node in the antegrade pathway in the diagram to the right as indicated by the wavy line and arrow As a result The R P interval (*horizontally shaded area*) of the return extrasystole (*indicated by arrow*) is short since conduction back to the atrium through the retrograde pathway is rapid

more slowly through the excitable pathway since these nodal fibers will now be more refractory This will result in a prolonged P R interval of the premature beat Conduction of the impulse in the antegrade pathway will be slow enough to allow a more complete recovery of excitability of cells in the retrograde pathway resulting in rapid conduction of the re entering impulse back to the atrium The P R interval will be long but the R P interval will be short A definite reciprocal relationship occurs between the R P and P R intervals for re entering impulses of ventricular origin [24]

The electrocardiographic characteristics of some paroxysmal supraventricular tachycardias suggest that they result from continuous AV nodal re entry [25,26] These tachycardias are initiated by a spontaneously occurring premature atrial depolarization only when the premature impulse is conducted with marked delay in the AV node

Sinus node re entry Re entry can occur in the sinus node by the same basic mechanisms described for the AV node A premature impulse propagating into the sinus node can result in a functional dissociation of the node into several conducting pathways due to a disparity in the refractory periods of different sinus nodal cells [27] In addition the sinus node is surrounded by a zone of cardiac fibers with electrophysiological properties intermediate between those of sinus nodal fibers and atrial fibers This perinodal re

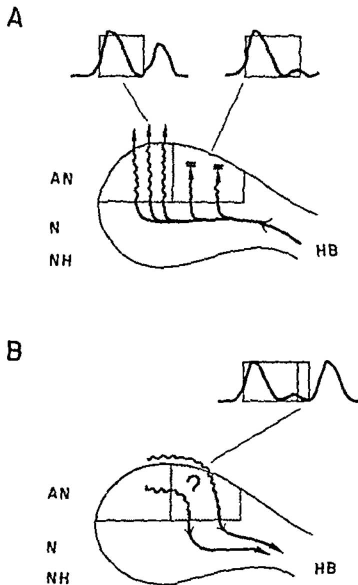


Fig 6 A and B Re entry of a ventricular impulse in the AV node The diagram of the AV node is the same as in Fig *5* In *A* action potentials recorded from the same two regions of the AV node as in Fig *5* are shown at the top The premature ventricular impulse again blocks in the region with the *longest refractory period while conducting through the* region with the shorter refractory period as indicated by the arrows *Panel B* shows the continuation of these events The impulse which conducts through part of the node can return to excite the area of the node in which it blocked and then re turn to the ventricle as indicated by the arrows It is uncertain whether the conducting impulse from the ventricle en *ters the return pathway to the ventricle within the* upper node or in the atrium Action potentials recorded in the re turn pathway are shown at the top

Presumably re entry then may occur by the mechanism described above

Impulses originating in *the ventricles can re* turn to the ventricles as a result of re entry in the AV node Experimental evidence suggests a similar mechanism and similar pathways for re *entry of ventricular* impulses in the AV node as for re entry of atrial impulses [19] A premature ventricular impulse will result in the dissociation of the upper nodal region into two functional pathways (Fig 6*A*) The premature impulse will conduct through the lower nodal region to the upper node The impulse will enter the cells in the upper node with the *shorter refractory period* while blocking in the cells with the longer refrac tory period It will conduct through the former *groups of fibers and then enter the previously* refractory fibers and return to the ventricles (Fig 6*B*) There is a disagreement as to the route *through which* conduction proceeds from the retrograde pathway into the antegrade path way [22,23] The atrium (or only a small region of atrium adjacent to the AV node) may be utilized, or there may be connecting bridges within the upper AV node Conduction of the re entering impulse in the upper node must be sufficiently slow to allow for *the recovery of excitability of* the lower nodal pathway (final common path way) *If the impulse conducts too rapidly through the pathways in the upper region of the node it* will return to the final common pathway before it recovers excitability and conduction of the re en *tering impulse will be blocked before it returns to* the ventricle [19]

Continuous re entry of ventricular impulses *through the AV node presumably can also occur* by a mechanism similar to the one described for the atrium

Electrocardiographic correlates of AV nodal re entry The conduction characteristics of the re entrant pathway in the AV node dictate the elec trocardiographic characteristics of AV nodal *re entrant* impulses One electrocardiographic feature which might occur on the basis of these conduction properties is a reciprocal relationship *between the P R interval of the sinus impulse* or premature atrial impulse immediately preceding the re entrant atrial activation (return extrasys *tole) and the R P interval of the re entrant* atrial activation (Fig 7) Premature impulses occurring relatively late in the atrial cycle but which block *in part of the upper AV node may* conduct rapidly through the excitable pathway and enter the retrograde pathway while it is still partially *refractory Conduction back* to the atrium would therefore be slow (Fig 7) As a result the P R in terval will be relatively short while the R P of the *return extrasystole* will be prolonged If the pre mature impulse occurs early in the atrial cycle it will block in part of the upper node but conduct

tory period of Purkinje fibers at the gate will block in each terminal twig and thus not reach ventricular muscle (Fig 8) Localized disease or ischemia may cause the action potential duration and effective refractory period of Purkinje fibers in some terminal twigs to become quite short [32] Purkinje fibers in other terminal twigs may not be influenced and these parameters remain normal When this occurs conduction of a premature impulse with a coupling interval shorter than the effective refractory period of Purkinje fibers at normal regions of the gate will block in these normal areas before ventricular muscle is activated (Fig 8) However, in terminal twigs where Purkinje fibers at the gate have short action potential durations and short effective refractory periods this premature impulse may conduct into the ventricular muscle From here it may propagate in a retrograde direction to reactivate the terminal twigs where block had occurred, and then conduct back into the ventricular conducting system as a re entrant impulse (Fig 8) The gate regions in peripheral Purkinje fiber ramifications which have normal effective refractory periods and where propagation of the premature impulse is blocked function as sites of unidirectional conduction

Re entry due to unidirectional conduction block at Purkinje fiber-muscle junctions Terminal Purkinje fibers of the ventricular conducting system make contact with ventricular muscle through low resistance intercalated discs It has been postulated that the functional geometrical arrangement of such junctions between terminal Purkinje fibers and ventricular muscle is in the form of a funnel whereby a cable of Purkinje fibers continues into a two or three dimensional irregular syncytium composed of ventricular muscle fibers [33,34] In such a system propagation from Purkinje fibers into muscle requires that the current from the cable like Purkinje terminals would have to excite increasingly larger areas of membrane as the impulse propagated into the ventricular muscle This lowers the safety factor for antegrade propagation at the Purkinje fiber-muscle junction The safety factor at different junctions will vary depending on the exact geometry which also may differ at the different junctions [35] The safety factor is even lower in the presence of partial depolarization or premature activation and as a result conduction block at the Purkinje fiber-papillary muscle junction may occur The safety factor for conduction in the retrograde direction at the same junctions (ventricular muscle to Purkinje fibers) is not as low since the impulse is propagating from a region of large membrane area (and therefore large current density) to a region of smaller membrane area The current density therefore may be sufficient to excite the cable like Purkinje fiber terminals As a result conduction may be maintained at the Purkinje fiber papillary muscle junction in the *retrograde direction* under circumstances in which conduction in the antegrade direction fails The *Purkinje fiber muscle* junction thereby becomes a site of unidirectional conduction block [35]

Since the safety factor for propagation in an antegrade direction varies at different Purkinje fiber-muscle junctions a slowly conducting premature impulse may block in the antegrade direction at some junctions while conducting through others The junctions at which conduction of the premature impulse is blocked still can conduct in a retrograde direction and thereby offer a return pathway for the impulse which succeeded in propagating into muscle to conduct back into the ventricular specialized conducting system as a re entrant impulse [35]

A premature impulse which induces re entry usually conducts at a subnormal velocity However this velocity is usually still too high to enable the impulse to conduct back into a region which already has been excited This latter region would still be refractory and conduction will block Re entry is facilitated in this instance by a profound shortening of the refractory periods in the regions where antegrade conduction block occurs at the Purkinje fiber-muscle junction [35] Such a shortening occurs because of the electrotonic interactions between Purkinje fibers and ventricular muscle fibers The premature impulse conducting into a junctional region with a low margin of safety blocks because the current density is not sufficient to excite ventricular muscle ahead Therefore at the point of block there are regions of depolarized (Purkinje) and polarized (ventricular) cardiac fibers in juxtaposition During the plateau phase of the premature action potential when membrane resistance is high current will flow from the polarized region of ventricular muscle to the excited, depolarized region of Purkinje fibers This current flow will be in the repolarizing direction and will therefore

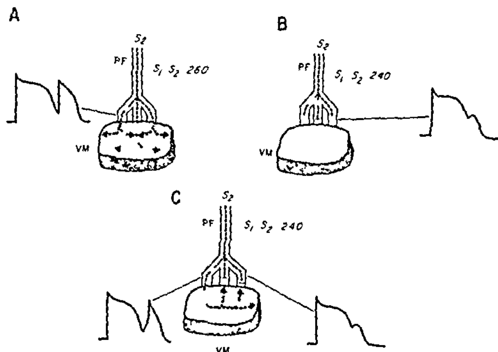


Fig 8 A B and C Re entry due to abnormalities in the gating mechanism The diagrams show a single bundle of Purkinje fibers (*PF*) branching into three bundles and then terminating on ventricular muscle (*VM*) In *A* action potential duration at the gate in each of the three short branches is identical A recording of one action potential is shown to the left When a premature impulse enters this region with a coupling interval (S_1 S_2) of 260 msec it can excite the Purkinje fibers at the gates in each branch and then activate ventricular muscle in the manner indicated by the dashed arrows In *B* at a slightly shorter coupling interval of 240 msec conduction of the premature impulse blocks at the gates and does not enter ventricular muscle The action potential recording at the right is representative of the events in all three branches *Panel C* shows the events which may occur if action potential duration at the gate in the left branch is shortened while duration remains normal in the other branches If a premature impulse now enters these distal branches at a coupling interval of 240 msec it will be able to excite the Purkinje fibers with the shortened action potential duration at the gate in the left branch (*action potential shown at left*) but conduction will still block at the normal gates in the other branches (*action potential shown at right*) Re entry may then occur as indicated by the dashed arrows The re entrant impulse reinvades the ventricular conducting system through the branches where antegrade conduction block occurred. (Modified from Myerburg R J Stewart J W and Hoffman, B F Electrophysiological properties of the canine peripheral AV conducting system Circ Res 26 361 1970 Reproduced by permission of the American Heart Association)

gion may also be a site for re entry [28,29] Atrial tachycardias resulting from continuous re entry in or around the sinus node undoubtedly occur [30]

IV Re entry as a result of alterations in refractoriness

Re entry can occur as a result of local alterations or differences in the refractory periods of cardiac fibers with fast response activity An area of unidirectional conduction and slowing of conduction still is necessary but these changes are not the result of partial depolarization Rather, they result from conduction patterns of premature impulses in regions with different refractory periods Although this mechanism is probably responsible for atrial as well as ventricular arrhythmias,[31] the following discussion is confined to the ventricular specialized conducting system

Abnormalities in the gates of the ventricular specialized conducting system The action potential duration and effective refractory period of Purkinje fibers progressively lengthen from proximal to distal regions in the ventricular specialized conducting system An area of maximal action potential duration and refractoriness was called the gate by Myerburg and colleagues [32] In either ventricle the duration of the action potential and the effective refractory period at the gate are identical in each terminal ramification of a normal bundle branch, but values for the right ventricle usually are longer than those for the left [32] The gate in the peripheral ramifications of each bundle branch, under normal conditions, determines the effective refractory period for that part of the ventricular conducting system A premature impulse entering a fascicle of a bundle branch before the end of the effective refrac

before complete recovery of excitability and therefore conduction will be markedly slowed (Fig 9) In addition the action potential durations of adjacent fibers in the infarct are not homogeneous action potential duration and refractoriness are prolonged more in some fibers than in others Therefore conduction of early premature impulses may block in the regions with the longest action potential durations and refractory periods while conducting through regions with a shorter action potential duration and refractory period (Fig 9) If conduction through these latter areas is sufficiently slow the impulse can return and excite regions in which it initially blocked and return to its point of origin as a re entrant impulse[36] Continuous re entry through the infarcted region may also occur resulting in a ventricular tachycardia

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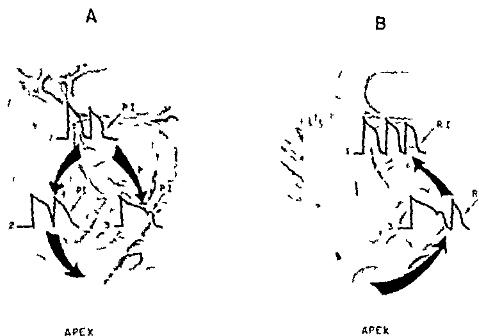


Fig 9 A and B Re entry in the subendocardial Purkinje fiber network surviving over an area of extensive myocardial infarction The diagram in each panel shows the left anterior papillary muscle (*at the left*) and anterior interventricular septum (*at the right*) The base of the heart is toward the top of the figure and the apex toward the bottom The lighter area which encompasses approximately two thirds of the papillary muscle and septum from apex toward the base is infarcted. The darker area toward the base is normal In *panel A* a premature impulse (*PI*) occurs at *site 1* at the border of the normal and infarcted region and conducts into the infarcted region in the surviving subendocardial Purkinje fiber network as indicated by the arrows The action potential duration of Purkinje fibers at *sites 2* and *3* in the infarct is prolonged and the action potential duration at *site 3* is longer than at *site 2* As a result, the premature impulse (*PI*) excites Purkinje fibers at *site 2* but conduction blocks at *site 3* as indicated by the action potential recordings *Panel B* shows a continuation of these events The premature impulse after conducting past *site 2* returns to activate the cells at *site 3* as the re-entering impulse (*RI*) and then conducts back to where it originated as the re entrant impulse (*RI*)

hasten repolarization of the premature action potential The duration and refractory period of the premature action potential at the region of block thereby will be markedly shortened enabling this region to be re excited earlier by the re entering impulse The refractory period may be reduced to as little as 50 msec [35]

Re entry in subendocardial Purkinje fibers surviving over areas of extensive myocardial infarction In the normal left ventricular interpapillary free wall anterior papillary muscle, or anterior septum, action potential durations and refractory periods of subendocardial Purkinje fibers are longest toward the base of the heart and decrease progressively toward the apex [36] Premature impulses which arise in the ventricular conducting system of the non infarcted heart will therefore propagate rapidly and uniformly from the base toward the apex Rapid propagation occurs because action potential and refractory period duration decreases in the direction of propagation and therefore the impulse is entering more fully repolarized fibers in the conduction pathway

In regions of extensive anteroseptal left ventricular myocardial infarction, the subendocardial Purkinje fiber network often survives possibly because it is nourished by blood from the left ventricular cavity and not completely dependent on the blood supply from the coronary arteries [37,38] The electrophysiological properties of such surviving subendocardial Purkinje fibers change markedly from normal The action potential duration throughout this subendocardial Purkinje network becomes extremely prolonged as does the effective refractory period of the surviving cells Due to this prolongation in the infarcted area action potential duration and refractory period now increase from the base of the left ventricle to the apex of the heart. Premature impulses arising *outside the infarcted* region *or* at the border of the infarcted and non infarcted area will propagate into these areas with longer action potential durations and refractory periods

Annotations

Trends in the incidence of disease in the United States

The incidence of disease in the United States is changing in response to the influence of public health measures the use of antibiotics economic growth aging and the increase in population density The incidence of infections bacterial and rickettsial diseases such as tularemia brucellosis typhoid fever typhus diphtheria and the like is approaching zero or an almost irreducible minimum Diseases which respond dramatically to antibiotic therapy such as the chronic diseases of syphilis and gonorrhea are ever decreasing in incidence and are controllable Primary and especially secondary and tertiary syphilis such as the syphilides aneurysm of the aorta aortic valvular insufficiency lesions of the central nervous system and in fact all forms of late syphilis are now becoming rarities and almost medical curiosities The serious complications of gonorrhea such as arthritis urethral stricture and the like occur much less frequently These drastic reductions in the incidence of venereal disease and especially the major late sequelae reflect the effects of education organized therapy and the use of antibiotics and other forms of medical services Malaria in the United States *is extinct* Intestinal parasites are rare and diseases preventable by vaccination and inoculation such as poliomyelitis are rarities

Viral diseases and fungal staphylococcal and certain bacterial infections are becoming more prominent as the incidence of most bacterial and protozoal diseases *declines* Nevertheless with better trained physicians and hospital care and the use of antibiotics the morbidity and mortality from complicating infections associated with all illnesses and major surgical procedures are declining rapidly Even rheumatic fever is less common less severe and less acute

Chronic degenerative diseases and the multiple diseases associated with the aging process are increasing however Senile arteriosclerosis and arterial hypertension with all of their many clinical manifestations are increasing as the number of old people increases (Table I) For example cerebrovascular diseases ischemic heart disease and renal disease continue to increase in incidence both clinically and as the causes of death As people are able to escape and overcome bacterial and some other infections they live long enough to develop eventually neoplastic diseases and the many chronic degenerative diseases of old age Even in the young age group the incidence of neoplastic diseases such as *leukemia is increasing* The collagen diseases such as lupus erythematosus disseminatus dermatomyositis acute vasculitis and arteritis and other diseases due to immunologic and so called auto immunologic reactions are becoming more common

The incidence of accidents and trauma along the highway rises Injury from physical trauma is still a major cause of illness and death in the United States This is attributable to the increase in population density industrial growth greater use of alcoholic beverages more rapid transportation by more powerful and greater numbers of automobiles and the ever increasing use of gadgets in the home in business and in recreation These hazards to human health and trauma to heart and blood vessels are now receiving greater attention in research public health programs and education

Table I Mortality from selected causes—United States*

Cause	*1900*	*1910*	*1920*	*1930*	*1940*	*1950*	*1960*	*1969*
All causes	1 308 134	1 356 528	1 382 892	1 393 352	1 417 288	1 452 454	1 711 982	1 921 990
All diseases of circulatory system including heart disease	115 206	171 599	200 796	293 045	413 968	745 074	923 635	1 013 015
Diseases of the heart	104 553	146 834	169 814	263 630	385 133	535 629	661 712	739 265
Cancer	48 700	70 414	88 793	119 877	158 398	210 733	267 627	323 092
Rheumatic fever	4 033	5 729	4 046	3 077	1 712	1 959	—	—
Syphilis	2 054	4 898	9 476	10 831	18 960	7 568	2 945	543
Leukemia	761	1 479	2 023	2 585	4 872	8 845	12 725	14 450
Alcoholism	4 033	5 082	1 065	4 303	2 502	2 267	—	—
Influenza	20 317	13 122	75 059	23 877	20 145	6 597	7 872	5 971
Diphtheria	30 666	19 498	16 289	6 031	1 448	410	—	—
Pneumonia	133 469	130 940	145 646	101 661	72 286	40 523	58 931	62 394
Tuberculosis, all types	147 927	142 121	120 413	87 508	60 436	33 959	10 866	5 567
Accidents	58 973	78 083	75 591	99 077	96 909	91 249	93 806	116 385

*Data obtained from "Vital Statistics Rates in the United States, 1900 1940 by F E Linder and R D Grove U.S. Printing Office Washington, 1947 Vital Statistics of the United States, 1950 Vol 1 PHS Vital Statistics National Summaries" Vol 54 No 1 1961 Vital and Health Statistics Series 20 No. 16 Department of HEW March 1974

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daily and dietary intake was observed over three day periods during each phase of the experiment In those subjects with higher triglyceride levels on the normal diet (> 120 mg per 100 ml) there was a significant fall of about 10 per cent in triglyceride levels during the sucrose free period while there was no significant change in triglyceride levels in the re maining subjects with lower triglyceride levels (< 120 mg per 100 ml) Such weight changes as did occur were not signifi cant and did not correlate with observed changes in lipid levels It was concluded that such reduction in serum triglyceride levels as did occur was due to the restriction of dietary sucrose

Others[11] have found that weight reduction and carbohy drate restriction are independent determinants of serum glyceride concentration and it has been demonstrated[12] that small falls in weight are not associated with a fall in fasting serum triglyceride concentration.

Reduction of the amount of sucrose in a diet is undoubtedly beneficial in that it causes weight loss In those with high serum triglyceride levels such a regime would also seem to have a direct lowering effect on serum triglyceride levels as well

A M Roberts MB BS
Medical Department
British Nuclear Fuels Ltd
Salwick
Preston Lancashire PR4 OXJ England

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New etiologies for ischemic heart disease

Studies of the causes of disease can be separated conve niently (if not too rigorously) into investigations of etiology and investigations of pathogenesis Pathogenetic studies are concerned with the physical and chemical mechanisms of the disease and the understanding of the internal environment the results (relationships with obesity hypertension serum cholesterol, clotting times in the case of ischemic heart dis ease) are of interest chi fly to therapists who hope that by changing the internal environment they can influence the course of the disease

Etiologic studies are concerned mainly with the genetic and environmental causes which precede recognizable dis ease and they interest chiefly the preventive specialist who hopes to interrupt the causal sequence before the disease de velops Etiologic studies of ischemic heart disease in recent years have concentrated very largely upon behavioral fac tors, especially tobacco smoking eating habits, and physical exercise and considerable efforts and expenditures have gone into attempts to modify behavior through health educa tion techniques. The progressive supression of cigarette ad vertising in many parts of the world is tangible evidence of a serious public interest and intent although it has been directed mainly against a less frequent fatal outcome of tobacco usage than ischemic heart disease Unfortunately few benefits of health education techniques have so far been demonstrated and regrettably few serious attempts to measure their eff ctiveness are being made

Against a background of uncertain prospects of success in this direction, attention has turned more and more to possi ble primary preventive measures which would not need to rely upon our uncertain abilities to change other people s behavioral patterns. Changes in the manufacture of cigarettes and in the manufacture of foods which alter their chemical properties without changing too much their famil iar physical properties (e g polyunsaturated margarines low tar-low nicotine cigarettes) are examples

Another possibility deceptively promising if interpreted too naively arose from the observation that mortality rates from ischemic heart disease were higher in districts with soft water supplies than in districts with hard water sup plies[1-9] Several investigators considered the possibility that the differences in ischemic heart disease mortality rates be

Air pollution by factories automobiles insect sprays and crowding in large cities is an increasing health hazard. The American home is a most heavily polluted site in America to day with tobacco smoke insect sprays deodorants cos metics, disinfectants detergents insecticides pesticides cleaning and polishing substances waxes drugs and home remedies and many other unnecessary materials brought into the home mainly as the result of the influence of adver tisements Most homes are more polluted than the surround ing city atmosphere Concentrated pollution of the respirato ry system with tobacco smoke continues to produce greater injury to the health of men and of ever increasing numbers of women, not necessarily by producing pulmonary neoplasia but by producing chronic bronchitis emphysema rhinitis, chronic paranasal sinusitis and general reduction in the vigor of physical and mental health Alcoholic intake is surely not benefiting the health of Americans and families and associates Unlike tobacco alcohol is a health hazard which not only injures the health and happiness of the user but also of his entire family friends and many others It reduces the quality and quantity of productivity of the user and too frequently that of his fellow workers

Mental illnesses are increasing in incidence in response to increase in population and the associated greater crowding greater competition in the endeavors of life and greater complexities of governmental activities and social upheaval The mental health of the people of the United States may be improving but the problems of mental health are becoming more evident and latent mental difficulties are becoming overt in response to the stresses associated with living in a vigorous complex and changing society Fewer people seem to be happy

The aging process with all of its multiple manifestations of various illnesses is becoming a greater problem as the num ber of old people increases The aging process is concerned primarily with cardiovascular respiratory renal and cerebral degenerative changes as the most serious problems. The infirmities loneliness and unhappiness of old age are major problems which need study and attack by health ser vices medical institutions federal state and local govern ments and other organizations in the United States These common diseases of the present influence the cardiac ill nesses and the practice of cardiology The cardiologist must be aware of the diseases associated with the heart disease of his patients

Nevertheless, in spite of all of the disease states mentioned above and the changing complexion of the incidence of dis ease in the U.S.A this country is one of the healthiest in the world in response to an ever increasing effort of its people to provide better and healthier living Lack of happiness re mains a major problem among people

George E. Burch, M.D
Department of Medicine
Tulane University School of Medicine
1430 Tulane Avenue
New Orleans La. 70112

Dietary sucrose and serum triglyceride levels

Although it is over a century since Lawes and Gilbert[1] showed that fat could be synthesized from dietary carbohy drates it is only 16 years ago that Yudkin[2] found a closer re lationship between coronary thrombosis and intake of sugar than any other nutrient he examined Later it was shown[3] that lipemia in man is more likely to be carbohydrate in duced than fat induced and it was suggested[4] that the type of carbohydrate eaten might be responsible for the increased incidence of ischemic heart disease in Yemenite Jews who had emigrated to Israel

More recently it has been reported[5,6] that patients with hy pertriglyceridemia have had their raised triglyceride values lowered by reducing their intake of dietary carbohydrate especially sucrose Closer investigation[7] of the effect of su crose revealed that it was the fructose moiety of the sucrose molecule that seemed largely responsible for the elevation of fasting triglyceride levels

Various studies[8,9] have been carried out into the effects of dietary sucrose restriction on fasting serum lipid levels over a period of several weeks In one study[8] 11 men who had suffered myocardial infarction and who had returned to work on anticoagulant therapy were instructed to avoid sucrose containing foods but no estimation was made of the sucrose content of their diets During the 10 week period of reduced sucrose intake significant falls of up to 25 per cent were ob served in serum triglyceride levels but these were accom panied by moderate though significant falls in weight In a second experiment[9] 51 healthy office workers were studied for 5¼ months These subjects were divided into three groups One group tried to avoid sucrose and another tried to halve their dietary starch intake Both these groups were asked to maintain their body weights by increasing their in take of other foods The third group acted as controls There was a significant reduction (of about 22 per cent) in the fast ing serum triglyceride levels in the low sucrose group but as there was also a reduction in weight the reduction of serum triglyceride levels was attributed in part, to the weight loss There were no significant lipid or weight changes in the low starch group

From these studies it was not possible to separate the effects of the loss of weight on the serum triglyceride levels from the effects of dietary sucrose restriction

In a more recent study[10] 18 healthy young men on an Ant arctic base were observed for 10 months For an initial period of four weeks they received a normal diet They were then put on an isocaloric virtually sucrose free diet for 14 weeks followed by a further period of 24 weeks on the normal diet During the sucrose free period the sucrose calories were replaced by glucose Serum samples were obtained at 14 day intervals for lipid estimation the subjects were weighed

daily and dietary intake was observed over three day periods during each phase of the experiment In those subjects with higher triglyceride levels on the normal diet (> 120 mg per 100 ml.) there was a significant fall of about 10 per cent in triglyceride levels during the sucrose free period while there was no significant change in triglyceride levels in the remaining subjects with lower triglyceride levels (< 120 mg per 100 ml) Such weight changes as did occur were not significant and did not correlate with observed changes in lipid levels It was concluded that such reduction in serum *triglyceride* levels as did occur was due to the restriction of dietary sucrose

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Medical Department
British Nuclear Fuels Ltd.
Salwick
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Another possibility deceptively promising if interpreted too naively *arose from* the observation that mortality rates from ischemic heart disease were higher in districts with soft water supplies than in districts with hard water supplies[1-9] Several *investigators considered the* possibility that the differences in ischemic heart *disease* mortality rates be

tween the hard and soft water areas could be secondary associations with unidentified social or dietary factors possessing geographical correspondences with soft water distributions However statistical standardization according to regional social differences have not in fact succeeded in reducing the strength of the association and the quoted studies cover a range of countries including The United States of America The United Kingdom Japan Sweden, and Canada This association has been reported also in Eire [10] The original observations on mortality differences have been strengthened by the demonstration of differences in the occurrences of cardiac pathology discovered at autopsy after accidental death in hard and soft water areas together with a demonstration of differences in blood pressures and plasma cholesterol levels in these areas [11 12]

Several mechanisms for a supposed effect can be postulated The calcium supplement of hard drinking water possibly concentrated upon boiled vegetables might interfere with the absorption of fat and reduce the incidence of significant atherosclerosis [13] Alternatively a calcium supplement might reduce the incidence of fatal arrhythmia Anderson Le Riche and MacKay[9] showed that the excess of ischemic heart disease deaths in soft water areas of Ontario were associated especially with sudden deaths reported to coroners However not all of the possible hypotheses are dependent upon the calcium actually swallowed and the soft water effect could be related to plumbosolvency Crawford and Crawford[14] found higher bone lead contents in cases of accidental death occurring in soft water areas than in hard water areas

A recent statistical study in England and Wales[15] pursued these issues beyond the examination of water supplies to the examination of dietary intakes of calcium and other nutrients The dietary data were obtained from national nutritional sample surveys and the regional and annual variations of intake of 13 different nutrients were correlated with corresponding variations in the Standardized Mortality Ratios (SMR s) for ischemic heart disease Of the nutrients tested calcium gave the strongest correlation with a value of $r = -0\ 68$ implying a strong protective effect This degree of correlation is of the same order as that observed in several of the water supply studies Two other nutrients produced superimposed independent effects fat with $r = +0\ 56$ and, more surprisingly vitamin D with a similar positive (i e toxic) correlation of $r = +0\ 31$ Each of these correlations was obtained following statistical standardization for the effect of the previous nutrient

The positive correlation with fat intake makes good pathophysiologic sense and tends to support the meaningfulness of the other results The calcium effect could reasonably represent a fat absorption inhibition effect as suggested by Yacowitz and associates [13] The pattern would also correspond well with a lead absorption protection hypothesis since vitamin D operates in the reverse direction from calcium vitamin D is a known potentiator of lead absorption [16] and calcium an antagonist Dalderup[17] has suggested on the basis of experiments in rats that vitamin D could be directly toxic

However the dietary study included the precaution of examining SMR s for a series of other diseases in a like manner including diabetes cerebrovascular disease chronic bronchitis cancer of the stomach and deaths from all causes In each case a recognizably similar pattern of correlations with the 13 nutrients appeared and most of the nutrients showed similar "effects upon each of the diseases In addition general mortality levels and dietary calcium intake both follow fairly systematic geographical gradients with known social correlations which might explain them as a joint effect A review of the various hard and soft water supply studies reveal that similar joint associations with several diseases were recorded here For example Schroeder[1] found negative correlations between water hardness and cerebrovascular disease and several different cancers as well as cardiovascular disease Crawford Gardner and Morris[7] found negative correlations with bronchitis all cancers and several individual cancers including stomach cancer and with deaths from all noncardiovascular causes Turner[18] found similar associations with cancer of the stomach diabetes and cerebrovascular disease Lowe Roberts and Lloyd[19] and Fedrick[20] demonstrated similar associations for anencephalus

These various dietary and water associations with other vascular and nonvascular diseases do not in themselves demolish the hypothesis of an effect of calcium intake upon mortality rates from ischemic heart disease and do not prevent us from contemplating randomized trials Indeed, the complexity of the situation suggests that randomized experiments may be the only means of settling the matter However the results of the regional dietary studies suggest that the full picture may have an indirect explanation and dampen somewhat our hope that we might easily influence mortality either by a simple dietary calcium supplement or by manipulating the calcium content of water supplies

Prof E G Knox
Health Services Research Centre
Department of Social Medicine
University of Birmingham
England

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Marked variability of systolic heart murmur associated with idiopathic hypertrophic subaortic stenosis

Variation in the severity of left ventricular outflow tract obstruction in response to physiologic and pharmacologic maneuvers is characteristic of idiopathic hypertrophic subaortic stenosis (IHSS) and useful in distinguishing it from other types of cardiac disease [1, 2] Major differences in the magnitude of the systolic pressure gradient may occur spontaneously during the course of a single left heart catheterization [1, 3] and variation in intensity of the associated systolic ejection murmur from one examination to the next has been described.[2] We recently studied a patient with IHSS in whom the intensity of the systolic murmur varied markedly during continuous auscultation.

J H a 46 year old male was admitted to the Salt Lake Veterans Administration Hospital on July 24 1973 He had noted minimal exertional dyspnea for five years and had recently had two episodes of severe dyspnea during mild exertion, one of which was associated with chest pain On physical examination the pulse rate was 70 and sitting brachial blood pressure was 165/95 mm. Hg The carotid upstroke was extremely sharp and fast rising and the left ventricular (LV) impulse was prominent with a palpable double impulse A fourth heart sound was heard, and there was a long systolic ejection murmur heard best at the lower left sternal border No other murmurs were heard.

During auscultation with the patient relaxed in the supine position it became apparent that the murmur was varying markedly (from Grade I/VI to Grade IV/VI) and frequently in intensity remaining at a given intensity for a few seconds to several minutes before changing The variation in intensity was independent of respiration or heart rate This phenomenon was confirmed by several observers and clearly documented by phonocardiogram During periods when the murmur was stable it increased in intensity following a premature beat and during a Valsalva maneuver and decreased in intensity with sudden squatting

An echocardiogram was interpreted to show increased thickness of the interventricular septum and abnormal systolic movement of the anterior mitral valve leaflet toward the septum During cardiac catheterization there was no resting pressure gradient between the LV cavity and the brachial artery (BA) but a 55 to 125 mm Hg pressure gradient was demonstrated during isoproterenol infusion and on post PVC beats There was no gradient between the LV outflow tract and the ascending aorta The BA pulse pressure on beats following premature beats was either decreased or unchanged No mitral regurgitation was seen on LV angiogram

The precise mechanism of the extreme variability in the intensity of the murmur in our patient is unknown It presumably reflects the fact that the dimensions of the LV outflow tract are not fixed but may be influenced by a number of variables including the contractile state of the myocardium venous return, and systemic arterial pressure [1] The reason for such frequent changes in one or more of these parameters in a resting patient is unclear Such spontaneous variability in intensity of a murmur consistent with obstruction to LV outflow may be a useful clue to the diagnosis of IHSS

Dennis Bauman M D
Salt Lake Veterans Administration Hospital
and The Department of Medicine
University of Utah College of Medicine
Salt Lake City Utah

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Letters to the Editor

Venospasm during cardiac catheterization

To the Editor

The problem of venospasm during cardiac catheterization is fairly common Occasionally we have been faced with a situation where even incision antegrade up the vein does not enable movement of the catheter In these cases we have been able to free the catheter by giving the patient sublingual nitroglycerin Although the vasodilatation is short lived it will enable the removal of the catheter and at tempts can then be made to find another suitable vessel In our experience this has proved to be a rapid and easily available solution to an exasperating problem and we hope might benefit others faced with venospasm during cardiac catheterization.

Mallan G Morgan, M D
Cardiology Fellow
Stephen P Glasser M D F A C P F A.C.C.
Associate Professor of Medicine
Chief Cardiology Section
Fellow of the
Council on Clinical Cardiology of the American Heart Association
Louisiana State University Medical Center
Shreveport, La. 71130

Fever in relation to serum enzyme changes in acute myocardial infarction

To the Editor

I read with interest Dr Gibson s article The significance of fever in acute myocardial infarction A reappraisal (Am Heart J 87 439 1974)

Dr Gibson s results show no correlation of maximal rectal temperature with serum glutamic oxaloacetic transaminase (SGOT) level, except in the group of patients below age 70 who had subendocardial infarction, and he concludes that the degree of fever unrelated to infection in acute myocardial in farction is not associated with the mass of myocardium in volved, and is probably a non specific pyrogenic reaction re quiring a relatively small critical mass of infarcted tissue However it may be that the maximal temperature is not the best index of the febrile response and it is of interest in this respect that in animal experiments it has been shown that, after intravenous injection of human endogenous pyrogen, fever area is rather more closely related to the dose of pyrogen than fever height.[1]

I would like to report a study that I carried out at Bradford Royal Infirmary in which the size" of fever (a measurement which takes into account the time course as well as the height of the fever) was related to serum enzyme changes in acute myocardial infarction. The patients were all those admitted to the coronary care unit during a six month period in whom a di agnosis of acute myocardial infarction was established by standard clinical, electrocardiographic and serum enzyme ab-

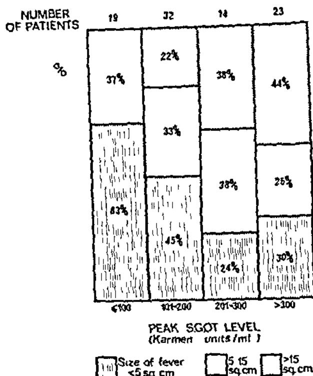


Fig 1 *Relation between size of fever and peak SGOT level in patients with acute myocardial infarction who developed fever*

normalities Patients who died during the first five days after admission to hospital, or who developed an infection or other cause of fever not directly related to myocardial infarction, were excluded because the fever pattern was distorted. Oral temperature was measured four hourly and fever was charted on 1 cm graph paper with 2 cm on the vertical axis for each 1 C and 2 4 cm on the horizontal axis for each 24 hours the area enclosed by the fever curve above a baseline at 37 2 C (the size of the fever) was measured planimetrically in square cm. Peak SGOT level (in Karmen units/ml.) was taken from measurements made on three successive mornings after ad mission to hospital.

There were 117 patients and fever developed in 88 (75 per cent) There was no relationship between maximal oral tem perature and peak SGOT but the size of fever and peak enzyme level (as shown in Fig. 1) were found to be signifi cantly associated (using chi square test with Yates s correc tion $\chi^2 = 13\ 51$ $P < 0\ 05$)

There is considerable evidence that peak SGOT level is re lated to the size of the infarct, both from studies of experimen tal myocardial infarction in animals[2-4] and from postmortem studies in man.[5] I would like to suggest that the present results indicate that the size of fever but not the maximal tempera ture may be related to the mass of myocardium infarcted, as reflected by the SGOT level The size of fever can of course only be measured retrospectively and therefore is of no value

in assessing immediate prognosis in acute myocardial infarction

R L Woodhead M A BM M R C P*
Bradford Royal Infirmary
Duckworth Lane Bradford
Yorkshire BD9 6RJ England

Present address University Department of Medicine The General Infirmary Leeds LS1 3EX England

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Book reviews

Treatment of cardiac emergencies By Emanuel Goldberger M D St Louis 1974 The C V Mosby Company 355 pp

Goldberger s book on treatment of cardiac emergencies is concisely and lucidly written The discussions reflect the author s approach to the emergencies except for a chapter on acute dissecting aneurysms of the aorta written by Wheat. The common emergencies are discussed from the practical clinical points of view The book therefore should interest all medical students house staffs and practicing physicians Practicing physicians will find the manual useful since the emergency states are discussed concisely The discussions of the common drugs used for cardiac emergencies are practical. The actions side effects indications dosage and interactions with other drugs constitute an important aspect of this book for the emergency room physicians Numerous medical emergencies are cardiac therefore this book should be studied by emergency room physicians

Recent advances in studies on cardiac structure and metabolism Myocardial metabolism Edited by N S Dhalla and G Rona Baltimore 1974 University Park Press, vol 3 878 pp

Volume 3 on myocardial metabolism is another excellent publication on an extremely important subject in medicine The many contributors have presented an extensive review of the state of knowledge and recent advances in myocardial metabolism The main topics discussed include cyclic AMP cardiomyopathy cardiovascular pharmacology myocardial hypertrophy and myocardial ischemia Many general topics are also presented. These were presented by contributors from all over the world. This series of topics should interest all cardiologists physiologists pathologists and pharmacologists It is a highly recommended book which contains the proceedings of the Fifth International Study Group for Research in Cardiac Metabolism held in Winnipeg Canada during June 1972

Recent advances in studies on cardiac structure and metabolism Vol 2 Cardiomyopathies Edited by E Bajusz and G Rona Baltimore 1973 University Park Press 842 pp

The proceedings of the International Symposium on Cardiomyopathies in Tiervlei South Africa, in 1971 are contained in this volume 2 on cardiac structure and metabolism The cardiomyopathies constitute an important aspect of cardiac disease Over 20 per cent of heart disease in certain areas of the world are reported to be cardiomyopathy It is a fairly common disease in the USA and Europe as well This volume rather extensively reviews the cardiomyopathies from both the experimental and clinical points of view The reader will find this book to contain the important aspects of cardiomyopathy as viewed by laboratory investigators, pathologists and clinicians from many parts of the world The discussions are extremely interesting and informal This valuable book should interest everyone concerned with the heart and circulation.

Blood flow and microcirculation. By Stanley E. Charm Sc D and George S Kurland, M D New York, 1974 John Wiley & Sons Inc 243 pp $18 00

This book by Charm and Kurland will appear to be too complex for practicing physicians but it does contain important physiologic information which has clinical applications and needs serious consideration. There is a lack of knowledge among physicians concerning the microcirculation It is the capillaries which are related to the blood supply to cells and, in addition they are extremely complex. Physicians seem to think only in terms of the big vessels failing to realize that the small vessels are there and many factors influence this function This book in relatively simple terms summarizes briefly the hemodynamic factors concerned with regulation of blood flow in small vessels The mathematics will frighten clinicians This should not deter a careful study of this book In fact the mathematical expressions are only approximations anyway since all variables are not known and many are based on important assumptions This does not mean that attempts to express the circulation in mathematical terms should be discouraged. Regardless, this is a good book that emphasizes the importance of factors which modify the peripheral circulation. For example it was not many years ago when physiologists indicated that viscosity should be ignored and hematologists taught that it was constant The authors develop these concepts very well

Microangiography of the lung in infancy and childhood By Bengt Robertson, Stockholm 1973 Proprius 86 pp

The circulation to the lungs has received relatively little attention Its importance is evident when it is realized that all the blood that circulates through the systemic circulation must pass through the blood vessels of the lungs Pulmonary vascular disease is almost entirely limited to consideration of pulmonary embolism by practicing doctors. However other diseases also modify the pulmonary circulation These pulmonary vascular diseases and certainly the normal circulation need more attention Robertson has very clearly presented a study of the pulmonary vessels of young people which should interest all pediatricians and other doctors as well The illustrations and discussions clearly indicate the importance of the value of a thorough knowledge of the vasculature of the pulmonary circulation in health and disease

Books received

Mortality Trends for Leading Causes of Death (United States 1950 69) U S Dept of Health Education & Welfare Rockville Md 1974 Public Health Service Health Resources Administration U S Government Printing Office 75 pp

√**Methods of Clinical Examination A Physiologic Approach, 3rd ed of Physical Diagnosis** Edited by Richard D Judge M D and George D Zuidema M D Boston Mass 1974 Little Brown & Company 405 pp $11 50

√**The Care of Patients Concepts and Tactics** By Mark Lipkin, M D New York 1974 Oxford University Press 265 pp $8 95

Safe Central Venous Nutrition By Mohamad H Parsa M D Jose M Ferrer M D and David V Habif M D Springfield, Ill 1974 Charles C Thomas Publisher 245 pp $17 50

Advances in Cyclic Nucleotide Research vol 4 Edited by Paul Greengard Ph D and G Alan Robison Ph D New York 1974 Raven Press Publishers 455 pp $28 50

Handbook for Radiologic Technologists and Special Procedures Nurses in Radiology By Njeta Whitman Powell R N Springfield Ill 1974 Charles C Thomas Publisher 96 pp $8 75

Announcements

The eighteenth annual Mid Winter Conference on Chest Disease

The Intermountain Thoracic Society will sponsor the eighteenth annual mid winter conference on chest disease January 22 25 1975 at the Snowbird Ski Resort The traditional conference will feature excellent medical education with prime time skiing in the alpine atmosphere of the famed Alta ski area 30 minutes from Salt Lake City Utah Internationally recognized medical authorities will treat the following topics Immunologic Lung Defense Mechanisms, Immune Disease of the Lung Respiratory Intensive Care Frontiers of Cardiopulmonary Support Biomedical Intensive Care Monitoring The conference begins the evening of January 22 There is limited registration For further information and applications contact Franklin K Brough Executive Secretary Intermountain Thoracic Society 1616 South 11th East Salt Lake City Utah 84105 or telephone (801) 484 4456

Cardiology symposium

The University of Texas Health Science Center at Houston Division of Continuing Education, will present its annual cardiology symposium in Houston Texas on December 3 through December 5 1974 The program features selected topics in cardiology and the guest lecturer will be Bernard Lown M D Professor of Cardiology Department of Nutrition Harvard School of Public Health Boston, Mass.

For further information regarding the symposium please write The Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education P O Box 20367 Houston Texas 77025

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